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2004

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PROPERTIES OF SPHERICAL PELLETS PRODUCED BY A HOT-MELT EXTRUSION AND SPHERONIZATION PROCESS

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by

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Dissertation

Presented to the Faculty of the Graduate School of

The University of Texas at Austin

in Partial Fulfillment

of the Requirements

for the Degree of

Doctor of Philosophy

The University of Texas at Austin

August, 2004

Dedication

To my parents

Acknowledgements

I wish to thank my family for making this endeavor possible. Mom and Dad, you shaped me into the person I am today. Although you joked with me about being a perpetual student, your love, support and encouragement were unwavering. I also appreciate the support of my brother and grandparents.

I would like to thank my supervisor, Dr. James W. McGinity, for his generous support, encouragement and guidance during my undergraduate and graduate studies at The University of Texas at Austin. I am sincerely grateful for his advice that was not limited to my academic and professional careers. I truly believe that his influence has made me a better person.

I am grateful to Dr. Robert O. Williams, III for his advice, expertise and encouragement. I would also like to thank the other members of my dissertation committee, Dr. Alan B. Combs, Dr. Isaac C. Sanchez and Dr. Christian P. Whitman, for their time and advice.

I would like to thank Dr. John J. Koleng for his guidance during my undergraduate and graduate studies. His enthusiasm and love of pharmaceutics set an example for me, and he was very influential in my decision to embark on this academic endeavor.

I am very grateful to Weijia Zheng for her advice and encouragement, both academically and personally. She has always supported me, even when times were rough. I feel extremely fortunate to have had her as a lab mate and friend during these 5 years.

I am grateful to my friends for their assistance and cooperation during my studies. Shirley, I appreciate you giving me a place to stay when I was homeless. I would also like to thank Matteo and Sara for their tremendous generosity, and Hector for his friendship.

Lastly, I would like to extend my appreciation to my recently graduated colleagues and friends: Dr. Feng Zhang, Dr. Chuanbin Wu, Dr. Michael Repka, Dr. Yucun Zhu and Dr. Diane Bruce. Furthermore, I would like to thank fellow graduate students for their support: Shellie Callahan, Caroline Dietzsch, Shawn Kucera, Dave Miller and Dorothea Sauer.

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Publication No._____

Christopher Ryan Young, Ph.D.

The University of Texas at Austin, 2004

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Melt-extrusion is an efficient, continuous and solvent-free process that has been studied to prepare granules, sustained-release tablets and transdermal drug delivery systems. The research in this dissertation investigated the physicochemical properties of spherical pellets produced by a novel melt-extrusion process.

Pellets are widely employed in controlled-release systems. Wet-mass extrusion and spheronization is the more established method of producing spherical pellets, but this technique utilizes water and requires additional processing steps to produce controlled-release beads. Thus, a novel melt-extrusion technique was characterized to manufacture spherical pellets, and the controlled drug release properties of the resulting beads were examined. Furthermore, the physical properties of matrix pellets produced by either wet-

mass or melt-extrusion were investigated, including morphology, porosity and particle size distribution.

Although marketed controlled-release dosage forms exhibit significant differences in the design and composition, these preparations can be broadly categorized as single or multiple unit systems. Multiple unit dosage forms offer several advantages, such as improved bioavailability and reduced risks of dose dumping, local irritation and tampering. The physical and drug release properties of tablets compressed from melt-extruded pellets were investigated. Furthermore, the influences of compression force, filler excipient and pellet to excipient ratio on the properties of pellet containing compacts was investigated using drug release, hardness, friability and disintegration time determinations.

The physicochemical properties of a melt-extruded system containing poly(ethylene oxide) and guaifenesin were studied. The calculated Hansen solubility parameters and thermal properties of materials were used to determine suitability of systems for thermal-processing. Following extrusion, the influence of accelerated storage conditions on the drug release and physical properties of pellets was studied. Furthermore, film-coating of melt-extruded beads with Eudragit® L 30 D-55 was studied to design a melt-extruded pellet system with pH-dependent drug release properties.

Melt-extrusion processes were studied to manufacture controlled release matrix systems based on Acryl-EZE®, which is a pre-mixed excipient blend based on a methacrylic acid copolymer. The physical and chemical stability of materials during thermal processing was studied using thermal gravimetric analysis and HPLC. Modeling of drug release and swelling/erosion studies were

employed to determine the influence of swelling agents on the mechanism and kinetics of drug release from thermally processed dosage forms.

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Chapter 1: Introduction

1.1 CONTROLLED-RELEASE DRUG DELIVERY SYSTEMS

1.1.1 Controlled-release drug therapy

Conventional drug therapy involves the periodic dosing of a therapeutic agent that has been formulated to ensure stability, activity and bioavailability of the active pharmaceutical ingredient (API). Nevertheless, many drugs present difficulties when administered by conventional methods due to toxicity and low therapeutic index problems. Controlled-release systems have been designed to maintain plasma drug levels in the therapeutic range and thus minimize the effects of such problems (Gandhi 1999, Sood 2003).

1.1.2 Design of controlled-release systems

The rate of drug input into the body or dosing rate is determined by the rate of drug release from the delivery device. Multiple kinetic models and equations can be used to describe the drug release kinetics from controlled-release systems, but formulations that give zero-order drug release in vivo are widely accepted as ideal form many drug therapies (Guinchedi 1989). However, controlled-release products have been studied to produce many different release profiles. Systems exhibiting first-order drug release kinetics are also frequently employed to achieve the goals of controlled drug release therapies.

Thus, a zero- or first-order release model is often considered when calculating the desired drug release kinetics (Ritschel 1988). The controlled drug release system is then formulated and developed to achieve the desired drug

release profile (Ritschel 1989). Although there are significant differences in the design and composition of marketed controlled-release dosage forms, these preparations can be broadly categorized as either single or multiple unit dosage forms.

1.1.3 Single unit dosage forms

Single unit dosage forms are defined as oral delivery systems that consist of one unit that contains a single dose of the drug and is intended to be administered singularly (Gandhi 1999). Many single unit dosage forms have been developed for the controlled-release of bioactive materials. The most widely investigated example is the monolithic matrix-based tablet (Katznendler 1997, Nellore 1998, Pickler 1998). The advantages of this dosage form include high drug loading and the availability of well-characterized and cost-effective production methods. Drug release from these systems is controlled by a variety of mechanisms, including drug diffusion, tablet erosion, matrix swelling or a combination of these mechanisms. Film-coated and osmogen controlled single unit dosage forms have also been studied for modified release applications (Cao 2004, Zang 2003).

1.1.4 Multiple unit dosage forms

The concept of the multiple unit dosage form was introduced in the early 1950s. These solid oral dosage forms consist of a multiplicity of small discrete particulates, which include mini-tablets, pellets and granules (Bodmeier 1994). These systems provide flexibility during formulation development and therapeutic benefits to patients. A significant advantage of multiparticulates is that they can be divided into desired doses without formulation or process

changes. They can also be blended to deliver simultaneously incompatible bioactive agents or particles with different drug release properties. Furthermore, these dosage forms are less susceptible to dose dumping than the reservoir or matrix type, single unit tablet since the drug release profile does not depend on the drug release properties of a single unit (Erkoboni 2003).

Pellets offer advantages as constitutes of multiple unit dosage forms since studies have indicated that they are rapidly and evenly dispersed in the gastrointestinal tract upon oral administration, thus maximizing drug absorption and reducing inter- and intra-subject variability due to differences in gastric emptying rates (Sandberg 1988). Pellets can be filled into hard gelatin capsules or compressed into tablets, which rapidly disintegrate into multiple units.

1.2 METHODS OF PELLET PREPARATION

Pharmaceutical pellets or beads are spheres of varying diameter that can be produced by several methods. Pellets usually range in size from 0.5-1.5 mm depending on the application, but systems have been reported that use pellets as large as 3.0 mm (Gandhi 1999).

1.2.1 Spray drying

Spay drying is a process in which an aqueous solution of core materials and polymer are atomized into hot air. The water evaporates and the dry solids separate into pellets. Researchers have noted that this technique produces hollow pellets when the liquid evaporates at a rate faster than diffusion of the dissolved substances back into the interior of the droplet. Additionally, dissolved substances can migrate to the droplet surface as the liquid evaporates, resulting in an internal void (Ghebre-Sellassie 1989).

1.2.2 Spray congealing

In spray congealing, a drug is dissolved or dispersed in a molten material that is sprayed into an air chamber where the temperature is maintained below the melting points of the sprayed materials. This process provides spherical congealed pellets (Ghebre-Sellassie 1989). The resulting pellets are held together by solid bonds formed from the congealed melts. Furthermore, the particles exhibit low porosity due to the absence of solvent evaporation during the spray congealing process (Hincal 1994).

1.2.3 Fluidized bed technology

Fluidized bed technology suspends a drug and core materials in an air stream to form a constantly agitated fluidized bed. Pellets are formed when a binder solution, suspension or melt is sprayed onto the fluidized powder bed (Wan 1996). However, control of this process is difficult. Wetting, drying, and mixing of particles occurs simultaneously in one apparatus. These different elementary processes affect each other and thus the influence of each phenomenon on the growth kinetics of granulation is difficult to characterize (Hemati 2003).

1.2.4 Layer building

Another technique used to prepare pellets is layer building. A solution or suspension of binder material and drug is sprayed onto the surface of an inert core. Multiple layers are often applied to achieve the desired dose. This process is efficient since pellets can be coated with a functional polymer in the same apparatus after layer building. However, this technique is limited to low dose

drugs since only small drug loadings can be effectively layered onto the core material (Chambliss 1989).

1.2.5 Wet-mass extrusion and spheronization

Wet-mass extrusion and spheronization is a multiple-step process for producing uniformly sized pellets. The process requires at least five units of operation including dry mixing, wet granulation, extrusion, spheronization and drying. After drying, screening may be required to obtain a narrow particle size distribution and coating is usually necessary for controlled-release applications.

The spheronization technique was invented by Nakahara in 1964 (Nakahara 1966), but it was not widely known until publication of the process by employees of Eli Lilly and Co. (Conine 1970, Reynolds 1970). A major advantage of this technique over other methods is the ability to achieve a high drug loading without producing an excessively large particle (Erkoboni 2003). Furthermore, researchers have noted that extrusion/spheronization processes usually exhibit high throughput and low wastage of materials (Gandhi 1999).

1.3 CONTROLLED DRUG RELEASE FROM WET-MASS EXTRUDED/SPHERONIZED PELLETS

Film-coating is widely used to modify the release of active ingredients from pellets. Materials that have been studied for the production of controlled-release coating include waxes, shellac, ethylcellulose, cellulose acetate, acrylic resins and silicone elastomers (Porter 2000). Although film-coating is the most frequently employed method of producing controlled-release pellets, the process is not without problems. This technique is labor intensive and costly since coating systems require water or solvent removal, which may include a post-coating drying or curing step at elevated temperatures. Additionally, drug release

profiles may not be reproducible due to variations in film-coating thickness (Andersson 2000) or imperfections in the coating that result from aging or cracking of the polymer film (Lippold 2001). Employing matrix pellet systems to control drug release may circumvent problems associated with film-coating (Gandhi 1999).

Cold-mass extrusion and spheronization techniques have been studied to produce controlled-release matrix pellets, which utilize an eroding matrix system or release retarding agents. Mehta et al. (2001) manufactured eroding matrix pellets using the acrylic polymers Eudragit® L 100-55 and Eudragit® S 100. Controlled-release pellets have also been produced using release-modifying agents such as hydrophobic components (Ghali 1989), cellulose-derivatives (Levis 2001), chitosan (Goskonda 1993) and pH adjusters (Bianchini 1992).

Nevertheless, many of these systems offer limited control of drug release or present processing difficulties. Furthermore, cold-mass extrusion and spheronization methods generally utilize water and require an energy demanding and time consuming drying phase. Reports have also demonstrated that drug release rates from matrix systems depend significantly on the processing technique and that matrix systems developed using thermal methods display slower drug release rates than systems produced by non-thermal methods (Onay-Basaran 1985, Billa 1998).

1.4 THERMAL PRODUCTION TECHNIQUES

1.4.1 Melt-granulation

The melt-granulation process is a single-step technique that converts fine powders into granules of various sizes. In particular, the powder agglomeration is

promoted by the addition of low melting point binders, including glycerides, fatty acids, polyethylene glycols and waxes. This process also requires that materials are stable at temperatures above the melting range of the binder (Holm 1997).

Melt-granulation is usually performed in high shear mixers which are capable of producing granules and pellets. Researchers have found that high shearing forces and long massing times generally promote the formation of near spherical pellets (Seo 2001) Heating jackets are usually applied to control the product temperature. However, it is difficult to maintain a constant temperature since the shearing forces raise the product temperature due to the heat of friction (Hamdani 2002). Also, the process is difficult to control since pellet sphericity is influenced by several formulation variables, including concentration of the binder (Heng 2000), the viscosity of the binder (Heng 2003) and the particle size of the binder (Schæfer 1996) and filler (Johansen 2001).

1.4.2 Melt-extrusion

In melt-extrusion applications, a drug is dissolved or dispersed in a molten binder. Various polymers and low molecular weight excipients such as sugars, sugar alcohols and waxes have been employed as thermal binders (Breitenbach 2002). This process offers advantages over conventional granulation methods since molten binders are employed instead of water or other solvents. The raw materials are forced through die to yield a product of uniform shape. When the process occurs at elevated temperatures, it is often referred to as hot-melt extrusion.

Melt-extrusion is a well studied method since it is a widely applied processing technique used in the plastics industry to produce tubes, pipes, wires and films. The intense mixing and agitation during processing cause suspended

drug particles to deaggregate in the polymer melt, resulting in a more uniform dispersion of fine particles (McGinity 2000). .Melt-extrusion is an efficient and continuous process (Liu 2001) that has been studied by pharmaceutical scientists to prepare granules, sustained-release tablets and transdermal drug delivery systems (Follonier 1994, Aitkin-Nichol 1999, Repka 1999, Zhang 1999, Zhang 2000). Furthermore, this technology leads itself to comprehensive documentation and process controls and thus satisfies regulatory authorities. Pharmaceutical products manufactured using melt-extrusion techniques have been approved in the USA, Europe and Asia (Breitenbach 2003).

1.5 MELT-EXTRUSION TECHNOLOGY

Melt-extrusion processes consist of three basic steps: melting or plasticating a solid material, shaping the molten material and solidification of the material into a desired shape. Mixing of additives and fillers is an additional function of some extrusion processes. Several types of downstream equipment are employed to further process the extrudate into the desired form.

1.5.1 Equipment

The polymer industry uses several different designs of extruders, but the main distinction between various extruders is their mode of operation: discontinuous or continuous (Rauwendaal 1994). Discontinuous extruders are equipped with a reciprocating member to deliver molten materials in an intermittent fashion, while extruders with a continuous mode of operation use a rotating member. Injection and blow molding are processes that employ discontinuous extruders. Examples of continuous equipment include screw, disk

and drum extruders. Most reported pharmaceutical applications of hot-melt extrusion have employed screw extruders.

Screw extruders are divided into single screw and multi screw extruders. The single screw extruder is the most important type of extruder used in the polymer industry due to its advantages of relatively low cost, straightforward design, ruggedness and reliability (Chung 2000). A vertical, single screw extruder is seen in Figure 1.1. The screw of conventional single screw extruders has three geometrically different sections (Figure 1.2). The first section is referred to as the feed section or solid conveying zone. The screw generally has deep flights in this zone, and the material in this section will be mostly in the solid state. The section closest to the die is called the pumping section or metering zone. The pumping action is generated by the shallow flights of the screw in this section. Furthermore, thermal material in this zone is in the molten state during melt-extrusion applications. The section of the screw that connects the conveying zone to the metering zone is called the melting or transition zone. Thermal material is melted or plasticated in this section. Additionally, the depth of the screw channel reduces in a linear fashion going from the conveying to the metering section. This transition in screw flight compresses material in the channel.

A basic function of melt-extrusion applications is shaping of molten materials. A die is attached to the end of the extruder barrel that gives shape to the final product. The objective of an extrusion die is to distribute the melt in the flow channel such that the material exits from the die with a uniform velocity. The design of extruder dies is influenced by several variables, including the

composition of the extrudate as well as the operating parameters of the extruder (Perdikoulias 2003).

The cross-section of extrudates often increases upon exiting the die due to a phenomenon known a die swell. In general, polymers that exhibit low Reynolds Number flows swell from 10% to 300% upon exiting the die, and this phenomenon depends on material composition, extruder speed, temperature and screw speed. This entropy driven event occurs as the individual polymer chains recover from the deformation imposed by the rotating screw by "relaxing" and increasing their radius of gyration.

Pelletization is a downstream operation of melt-extrusion processes in which molten materials that are pumped through a die are cooled and formed into pellets. Pelletizers are available in several different designs, but the resulting pellet is generally cylindrical in shape. Examples of strand and die face pelletizers are illustrated in Figure 1.3. Strand pelletizers cut a spaghetti-like strand using a bed knife and a milling-type rotor. The strands are usually cooled by passing through a water bath before being cut. In pharmaceutical applications, the cooling bath is often replaced with a cooling belt or static cooling table since many pharmaceutical products cannot contact water. Die face pelletization is an alternative processing method that cuts the strand at the die face in the molten form. The pellet is then cooled via air or liquid (Case 2003).

1.5.2 Materials used in pharmaceutical applications

In pharmaceutical applications, melt-extrusion equipment is used to disperse or dissolve an active ingredient and other functional excipients in a carrier material. Ingredients used to prepare pharmaceutical dosage forms are subject to strict purity and safety standards since the products are administered to

humans. Thus, most raw materials used in pharmaceutical melt-extrusion applications have also been employed in the production of dosage forms by conventional techniques (Repka 2000). In addition to these requirements, materials used in melt-extrusion applications must exhibit thermal stability during processing.

1.5.2.1 Thermal carriers

The material in which the drug is dissolved or dispersed is called the thermal carrier or binder. During extrusion, the carrier is usually transformed into a molten state. This phenomenon is termed melting when the solid material is crystalline and plasticating when the material is amorphous. In pharmaceutical melt-extrusion processes, the carrier substance is usually a polymer or low melting point wax. The heat due to friction generated by the screw is often sufficient to melt many low melting point waxes. Modulated differential scanning calorimetery (MDSC) and thermal gravimetric analysis (TGA) are often used to study the thermal properties of carriers employed in thermal applications.

The physical and chemical properties of the carrier significantly influence the drug release properties of the resulting dosage from. The waster solubility of the carrier material is critical when designing a controlled-release product. Researchers have found that the mechanism of drug release is primarily diffusion controlled from melt-extruded dosage forms containing water insoluble polymers and waxes such as ethyl cellulose (Crowley 2004) or carnuba wax (Sato 1997). Researchers have also studied systems containing water soluble polymers such as hydroxypropyl cellulose (Repka 2002), poly(ethylene oxide) (Zhang 1999) or polyvinylpyrrolidone (Follonier 1995) that control drug release by mechanism that is a combination of drug diffusion and matrix erosion. Furthermore, some

crosslinked materials such as Carbopol® polymers swell but do not dissolve in water. These materials form a three-dimensional structure that control diffusion of the active material (Perez-Marcos 1991).

The influence of medium pH and ionic strength on the solubility properties of carrier materials has also been studied. Eudragit® S is an ionic polymer based on methacrylic acid esters that exhibits solubility in aqueous media ≥ 7. Follonier and coworkers studied this polymer to modulate the release of diltiazem hydrochloride from dosage forms prepared using a hot-melt extrusion process (Follonier 1995)

The ionization of polymer networks containing carboxylic or sulphonic acid groups occurs as the surrounding medium rises above the pK_a of the ionizable moiety. Researchers have found that the swelling properties of ionizable gels are significantly influenced by both medium pH and ionic strength (Khare 1995). This property of ionizable gels can be employed to modify drug release rate. Refer to Table 1.1 for a list of carriers that have been used in melt-extruded dosage forms.

1.5.2.2 Plasticizers

A key feature of melt-extruders is their ability to efficiently melt and plasticate materials. When polymers are used, a polymer film is generated on the inner barrel surface as a result of heat conduction through the barrel. Rotation of the screw displaces the melt film and mixes the molten material into the bulk. In pharmaceutical applications, plasticizers are typically low molecular weight compounds. Researchers have noted that the incorporation of plasticizers into pharmaceutical polymers facilitate thermal processing, modify drug release properties and improves the surface appearance of dosage forms. Thermal

processing temperatures and times can often be reduced upon addition of a plasticizer, thus diminishing degradation of thermally labile components (Repka 1999).

Plasticizers improve the workability and flexibility of polymers by reducing the elastic modulus, tensile strength, melt viscosity and glass transition temperature (T_g) of the material. Four major theories have been proposed to explain the mechanism of plasticization, including the lubricity, gel, salvation-desolvation and free volume theories. The efficiency of plasticization depends on the chemical structure, molecule weight and concentration of the plasticizer. Sears and Darby (1982) discussed in detail the theories of polymer/plasticizer compatibility. The compatibility of polymers and plasticizers can be indicated by various parameters, including internal pressure, solubility parameter, dielectric constant and polarity parameter.

Drugs and other excipients used in pharmaceutical applications can sometimes be employed as plasticizers of polymers. Wu and McGinity (1999) reported that solid non-traditional plasticizers including methyl paraben and drugs such as ibuprofen and chlorpheniramine maleate were able to lower the glass transition temperature of polymeric films prepared from aqueous latex dispersions of Eudragit® RS 30 D. Zhu and coworkers (2002) studied a melt-extrusion process to prepare controlled-release tablets containing Eudragit® RS PO and chlorpheniramine maleate (CPM). The researchers found that the acrylic polymer was plasticized in situ by CPM during thermal processing.

1.5.2.3 Drugs

The physical and chemical properties of drugs often limit the formulation and processing options available for the development of controlled-release

dosage forms. Drugs often exhibit the potential for degradation due to hydrolysis when aqueous or hydroalcoholic media are employed during processing. Melt-extrusion offers benefits over many conventional granulating methods since water and other solvents are not required. Additionally, tablets of poorly compressible active ingredients that cannot be processed by traditional tableting equipment can be prepared by a melt-extrusion (McGinity 2003). However, the thermal properties of drugs processed by melt-extrusion are critical since many materials are thermally labile. Thus, the thermal stability of drugs used in melt-extrusion applications should be studied using techniques such as TGA and HPLC.

Met-extrusion forms a solid dispersion of one or more active ingredient in inert carrier(s) in the solid state. Solid dispersions can be classified as simple eutectics, solid solutions, glass solutions, glass suspensions, a compound or complex formation, amorphous precipitations in crystalline carriers or combinations thereof (Chiou 1971). Other researchers have defined solid dispersions based on drug solubility in the carrier material. When the drug is not soluble in the carrier material, the dispersion is termed a particulate dispersion or solid suspension. Drugs that exhibit solubility in the thermal carrier are dispersed on the molecular level and are called molecular dispersions or solid solutions (Dyar 2003).

Production of solid dispersion has been widely studied to reduce particle size and increase rates of dissolution (Bloch 1987). Traditionally, solid solutions of drugs have been prepared by melt or solvent evaporation methods. The resulting semisolid materials were hardened by cooling, pulverized, sieved, mixed with excipients and then filled into tablets or compressed into tablets.

These techniques were tedious and difficult to scale up. Melt-extrusion techniques are solvent-free and require fewer operations, and thus simplify the formation of solid solutions. Researchers used a melt-extrusion process to improve the solubility and dissolution rate of 17-estradiol hemihydrate (Hülsmann 2000). Polyethylene glycol (PEG) 6000, polyvinylpyrrolidone (PVP) and a vinylpyrrolidone-vinylacetate copolymer were used as carrier materials. The thermally processed solid dispersions exhibited a significantly increased dissolution rate of the drug when compared to physical mixtures of the drug.

A risk of molecular solid dispersions is conversion of the dissolved drug to the crystalline form since drugs usually exhibit limited solubility in polymers. However, morphologically stable melt-extruded solid dispersions have been prepared with drug loadings up to 60% (Breitenbach 2003). As illustrated in Table 1.2, several analytical methods have been employed to study the crystallinity of materials in a solid dispersion and to prove the quality and stability of the system.

The molecularly dispersed state of the drug can be stabilized by the matrix. Carriers with glass transition temperatures significantly above the storage temperature are generally preferred to produce stabile the solid dispersions. Additionally, the viscosity of the carrier material and intermolecular interactions between the drug and carrier are used to stabilize solid dispersions. Doherty and York (1987) studied a dispersion that was formed and stabilized by a hydrogen bond—furosemide—PVP interaction.

1.5.2.4 Functional excipients

Functional excipients used in melt-extrusion applications are broadly classified as release-modifying agents, bulking agents, processing agents and

miscellaneous additives. The selection and use of these excipients can impart specific properties to HME pharmaceuticals in a manner similar to those in traditional dosage forms (Zheng 1999, Repka 2000).

Traditional pharmaceutical excipients have been employed as thickening agents for melt-extrusion applications. Cuff and Raouf (1998) studied the influence of microcrystalline cellulose on the viscosity of the melt and the plasticity of the resulting extrudates of thermally processed matrices containing PEG 8000. Although microcrystalline cellulose functioned as a thickening agent, the incorporated drug, fenoprofen calcium, prevented hardening of the extrudate.

Various excipients have been studied to modify drug release rate from melt-extruded dosage forms. Follonier and coworkers (1995) found that the low porosity of melt-extruded dosage forms can result in incomplete drug release during dissolution testing. The researchers employed swelling agents and hydrophilic polymers to increase drug release rate by increasing matrix porosity. Furthermore, matrix systems often exhibit an initial burst in drug release due to solubilization of drug on the surface of the dosage form. The investigators found that viscosity inducing agents effectively reduced the observed bust effect.

Sprockel and coworkers (1997) used a melt-extrusion process to prepare disks containing theophylline suspended in polyethylene. Soluble additives were studied to increase drug release rate from the dosage forms. The agents studied, sucrose, NaCl and Plutonic F68, remained particulate during processing since they did not melt at the working temperatures. The studied additives increased the rate of theophylline release from the melt-extruded disks. The researchers noted that dissolution of the soluble additives increased the void fraction of the

matrix and thus increased the probability of forming a percolating pore continuous to the disk surface.

Polymers used as carriers in melt-extruded blends sometimes exhibit thermal degradation at the required processing temperatures. Oxidation is the primary pathway of degradation observed during melt-extrusion. The thermal stability of many materials that are susceptible to degradation can be improved with the addition of antioxidants, acid receptors and or light absorbers to the processed powder blends (McGinity 2000). Researchers studied the influence of antioxidants such as vitamin E and its derivatives, ascorbic acid and butylated hydroxyanisole on the thermal degradation of poly(ethylene oxide) during melt-processing (Crowley 2002), and they found that vitamin E, vitamin E succinate and vitamin E TPGS were suitable stabilizers of the polymer during processing.

Waxy materials such as glyceryl monostearate (GMS) have been studied as thermal lubricants during hot-melt extrusion. Henrist and coworkers (1999a, 1999b) investigated the influence of GMS concentration on the physical properties of melt-extrudates of starches and sugar alcohols. The researchers found that changing the composition of the formulation did not affect the water content or the porosity of the extrudates but that it did significantly influence the mechanical strength and dissolution properties of tablets. Furthermore, vitamin E TPGS has been reported to facilitate thermal processing by decreasing barrel pressure, drive amps, torque and the propensity for degradation of the API and other matrix components (Repka 2000).

1.6 RESEARCH OUTLINE

1.6.1 Overall objective

The overall objective of these studies was to characterize a novel melt-extrusion and spheronization process and to investigate the influence of thermal processing on the physicochemical and drug release properties of melt-extruded dosage forms.

1.6.2 Supporting objectives

1.6.2.1 Investigate the influence of production methods on the physicochemical and drug release properties of matrix beads

Wet-mass extrusion and spheronization is the more established method of producing spherical pellets, but this technique is not without problems since it utilizes water and/or other solvents, it is not a continuous processing method and it requires additional processing steps such as film-coating to produce controlled-release systems. Melt-extrusion is an efficient, continuous and solvent-free process that has been studied to prepare granules, sustained-release tablets and transdermal drug delivery systems. A novel and continuous melt-extrusion technique was characterized to manufacture spherical pellets, and the kinetics and mechanism of drug release from the resulting beads was examined using dissolution investigations and kinetic model fitting procedures. Pellets prepared using either wet-mass or melt-extrusion exhibited significantly different drug release properties. Thus, the physical characteristics of matrix pellets produced using different processing techniques were investigated, including morphology, porosity and particle size. The influence of storage conditions on the porosity, tortuosity and drug release properties of melt-extruded pellets was also studied.

1.6.2.2 Examine the impact of formulation components on processing parameters, physical properties and mechanisms of drug release from melt-extruded dosage forms

Materials used in melt-extrusion applications must exhibit thermal stability during processing. Furthermore, researchers have noted that reduction of the melting point or glass transition temperature of the carrier material facilitates thermal processing by decreasing barrel pressure, drive amps, torque and the propensity for degradation of the API and other matrix components. The suitability of formulations for melt-processing was determined using thermal gravimetric analysis and modulated differential scanning calorimetry. The chemical stability of extruded drugs was also verified using high performance liquid chromatography.

The solid-state solubility of the drug in the carrier material is important to consider when developing a solid dispersion since supersaturated systems bear the risk of reverting back to the more stable crystalline form, thus creating morphologically unstable products. A group contribution method was used to calculate the Hansen solubility parameters of materials and to predict drug/polymer miscibility. The morphological stability of melt-extruded beads was studied using powder X-ray diffraction and scanning electron microscopy.

Mixtures of polymers and excipients have proved useful in regulating the mechanism of drug release from matrix systems. The processability and the physicochemical properties of melt-extruded dosage forms based on a premixed polymer and excipient blend were investigated. The mechanism and kinetics of drug release were investigated using model fitting (Korsmeyer-Peppas, zero-order, first-order, Hixson-Crowell and Higuchi) and matrix hydration/erosion studies.

16.2.3 Investigate the influence of compression and film-coating on the physical properties, kinetics of drug release and physical aging of thermally processed drug delivery systems

Although marketed controlled-release dosage forms exhibit significant differences in the design and composition, these preparations can be broadly categorized as single or multiple unit systems. Multiparticulate dosage forms offer several advantages, such as improved bioavailability and reduced risks of dose dumping, local irritation and tampering. The influence of compaction on the drug release characteristics and physical properties of melt-extruded pellets was investigated surface area, porosity and dissolution studies. Furthermore, the effect of compression force, filler excipient and pellet to excipient ratio on the properties of pellet containing compacts was studied using drug release, hardness, friability and disintegration time determinations.

An advantage of melt-extruded beads over wet-mass extruded systems is that thermally processed beads can control drug release without a functional coating. However, film-coating is a useful and widely employed method of the pharmaceutical industry. Thus, a film-coating process was studied to design a melt-extruded pellet system with pH-dependent drug release properties. The stability of drug release from coated pellets was determined after storage for 1 and 3 months at 40°C/75% RH.

1.7 REFERENCES

Aitken-Nichol, C.; Zhang, F.; McGinity, J.W. Hot-melt extrusion of acrylic films. Pharmaceutical Research. 1996, 3, 804–808.

Andersson, M.; Holmquist, B.; Lindquist, J.; Nilsson, O.; Wahlund, K. Analysis of film coating thickness and surface area of pharmaceutical pellets using fluorescence microscopy and image analysis. Journal of Pharmaceutical and Biomedical Analysis. 2000, 22, 325-339.

Bianchini, R.; Bruni, G.; Gazzaniga, A; Vecchio, C. Influence of extrusion-spheronization on the physical properties of D-indobufen pellets containing pH adjusters. Drug Development and Industrial Pharmacy 1992, 18, 1485-1503.

Billa, N.; Yuen, K.; Peh, K. Diclofenac release from Eudragit®-containing matrices and effects of thermal treatment. Drug Development and Industrial Pharmacy. 1998, 24, 45-50.

Bloch, D.W.; Speiser, P.P. Solid dispersions—fundamentals and examples. Pharmaceutica Acta Helvetiae. 1987, 62, 23-27.

Bodmeier, R.; Paeraakul, O. Suspensions and dispersible dosage forms of multiparticulates. In *Multiparticulate Oral Delivery*, 1st Ed.; Ghebre-Sellassie, I., Ed.; Marcel Dekker: New York, 1994; Vol. 65, 143-158.

Breitenbach, J. Melt extrusion: from process to drug delivery technology. European Journal of Pharmaceutics and Biopharmaceutics. 2002, 54 (2), 107-117.

Cao, Q.-R.; Choi, H.-G.; Kim, D.-C.; Lee, B.-J. Release behavior and photo-image of nifedipine tablet coated with high viscosity grade hydroxypropylmethylcellulose: effect of coating conditions. International Journal of Pharmaceutics. 2004, 274 (1-2), 107-117.

Case, C.C. Melt pelletization. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 99-110.

Chambliss, W.G. Conventional and specialized coating pans. In *Pharmaceutical Pelletization Technology*, 1st Ed; Ghebre-Sellassie, I., Ed.; Marcel Dekker: New York, 1989; Vol. 37, 15-38.

Chiou, W.; Riegelman, S. Pharmaceutical applications of solid dispersion systems. Journal of Pharmaceutical Sciences. 1971, 60, 1281-1301.

Chung, C.I. *Extrusion of Polymers: Theory and Practice*, 1st Ed.; Hanser: New York, 2000; 1-50.

Conine, J.W.; Hadley, H.R. Preparation of small solid pharmaceutical spheres. Drug & Cosmetic Industry. 1970, 106, 38-41.

Crowley, M.M.; Zhang, F.; Koleng, J.J.; McGinity, J.W. Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion. Biomaterials. 2002, 23, 4241-4248.

Crowley, M.C.; Schroeder, B.; Fredersdorf, A.; Obara, S.; Talarico, M.; Kucera, S.; McGinity, J.W. Physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablets prepared by direct compression and hot-melt extrusion. International Journal of Pharmaceutics. 2004, 269(2), 509-522.

Cuff, G.; Raouf, F. A preliminary evaluation of injection molding as a technology to produce tablets. Pharmaceutical Technology. 1998, 22 (6), 97-106.

Doherty, C.; York, P.J. Evidence for solid- and liquid-state interaction in a furosemide-polyvinylpyrrolidone solid dispersion. Pharmaceutical Sciences. 1987, 76, 731-737.

Dyar, S.C.; Mollan, M. Melt-extruded particulate dispersions. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 261-276.

Erkoboni, D.F. Extrusion/Spheronization. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 277-322.

Follonier, N.; Doelker, E.; Cole, E. Evaluation of hot-melt extrusion as a new technique for the production of polymer based pellets for sustained release capsules containing high loading of freely soluble drugs. Drug Development and Industrial Pharmacy. 1994, 20, 1323–1339.

Follonier, N.; Doelker, E.; Cole, E.T. Various Ways of Modulating the Release of Diltiazem Hydrochloride from Hot-Melt Extruded Sustained-Release Pellets Prepared Using Polymeric Materials. Journal of Controlled Release. 1995, 36(3), 243-250.

Gandhi, R.; Kaul; C.L.; Panchagnula, R. Extrusion and spheronization in the development of oral controlled-release dosage forms. Pharmaceutical Science and Technology Today. 1999, 2 (4), 160-170.

Ghebre-Sellassie, I. Pellets: a general overview. In *Pharmaceutical Pelletization Technology*, 1st Ed; Ghebre-Sellassie, I., Ed.; Marcel Dekker: New York, 1989; Vol. 37, 1-13.

Goskonda, S.R; Upadrashta, S.M. Avicel RC-591/chitosan beads by extrusion/spheronization technology. Drug Development and Industrial Pharmacy. 1993, 19, 815-927.

Guinchedi, P.; Maggi, L.; Sangalli, A.; La Manna, A.; Conte U. Hydrophilic matrices for linear (zero-order) extended release of water-insoluble drugs. In: Proceedings of the 11th Pharmaceutical Technology Conference. 1989, 112–121.

Hamdani, J.; Moës, A.J.; Amighi, K. Development and evaluation of prolonged release pellets obtained by the melt pelletization process. International Journal of Pharmaceutics. 2002, 245, 167–177.

Hemati, M.; Cherif, R.; Saleh, K.; Pont, V. Fluidized bed coating and granulation: influence of process-related variables and physicochemical properties on the growth kinetics. Powder Technology. 2003, 130 (1-3), 18-34.

Heng, P.W.S.; Liew, C.V.; Gu, L. Influence of teardrop studs on rotating frictional base plate on spheroid quality in rotary spheronization. International Journal of Pharmaceutics. 2002, 241, 173–184.

Heng, P.W.S.; Wong, T.W.; Cheong, W.S. Investigation of melt agglomeration process with a hydrophobic binder in combination with sucrose stearate. European Journal of Pharmaceutical Sciences. 2003, 19, 381–393.

Hincal, Al; Kas, H.S. Preparation of micropellets by spray congealing. In *Multiparticulate Oral Delivery*, 1st Ed.; Ghebre-Sellassie, I., Ed.; Marcel Dekker: New York, 1994; Vol. 65, 11-34.

Henrist, D.; Remon, J.P. Influence of the formulation composition on the in vitro characteristics of hot stage extrudates. International Journal of Pharmaceutics. 1999a, 188 (1), 111-119.

Henrist, D.; Remon, J.P. Influence of the process parameters on the characteristics of starch based hot stage extrudates. International Journal of Pharmaceutics. 1999b, 189 (1), 7-17.

Holm, P. High shear mixer granulators. In *Handbook of Pharmaceutical Granulation Technology, Drugs and Pharmaceutical Science*, 1st Ed.; Parikh, D.M., Ed.; Marcel Dekker; New York, 1997; 151–204.

Hülsmann, S.; Backensfeld, T.; Keitel, S.; Bodmeier, R. Melt extrusion—an alternative method for enhancing the dissolution rate of 17-extradiol hemihydrate. European Journal of Pharmaceutics and Biopharmaceutics. 2000, 49, 237-242.

Johansen, A.; Schæfer, T. Effects of interactions between powder particle size and binder viscosity on agglomerate growth mechanisms in a high shear mixer. European Journal of Pharmaceutical Science. 2001, 12, 297–309.

Katzhendler, I.; Hoffman, A.; Goldberger, A.; Friedman, M. Modeling of drug release from erodible tablets. Journal of Pharmaceutical Sciences. 1997, 86 (1), 110-115.

Khare, A.R.; Peppas, N.A. Swelling/deswelling of anionic copolymer gels. Biomaterials. 1995, 16, 559–567.

Levis, S.R.; Deasy, P.B. Pharmaceutical applications of size reduced grades of surfactant co-processed microcrystalline cellulose. International Journal of Pharmaceutics. 230, 25-33.

Lippold, B.C.; Pagés, R.M. Film formation, reproducibility of production and curing with respect to release stability of functional coatings from aqueous polymer dispersions. Die Pharmazie. 2001, 49, 243-252.

Liu, J.; Zhang, F.; McGinity, J.W. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. European Journal of Pharmaceutics and Biopharmaceutics. 2001, 52, 181-190.

Mehta, K.A.; Kislalioglu, M.S.; Phuapradit, W.; Malick, A.W.; Shah, N.H. Release performance of a poorly soluble drug from a novel, Eudragit-based multi-unit erosion matrix. International Journal of Pharmaceutics. 2001, 213, 7-12.

McGinity, J.W., Koleng, J.J., Repka, M.A. and Zhang, F., 2000, Hot-melt extrusion technology. In *Encyclopedia Pharmaceutical Technology,* 2nd Ed.; Swarbrick, J.; Boilan, J.C., Eds.; Marcel Dekker: New York, 2000, Vol. 19, 203-226.

McGinity, J.W.; Zhang, F. Melt-extruded controlled-release dosage forms. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 183-208.

Nakahara. U.S. Patent 3,277,520, October 1966.

Nellore, R.V.; Rekhi, G.S.; Hussain, A.S.; Tillman, L.G.; Augsburger, L.L. Development of metoprolol tartrate extended-release matrix tablet formulations for regulatory policy consideration. Journal of Controlled Release. 1998, 50 (1-3), 247-256.

Onay-Basaran, S.; Olsen, J. Formulation of long acting quinacrine hydrochloride pellets in different matrices. Part 1. Drug Development and Industrial Pharmacy. 1985, 11, 2143-2154.

Perdikoulias, J.; Dobbie, T. Die design. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 99-110.

Picker, K.M.; Bikane, F. Tablet formation and release from matrix tablets manufactured with cellulose acetate. International Journal of Pharmaceutics. 1998, 175 (2), 147-164.

Porter, S. Coating of pharmaceutical dosage forms. In *Remington: the Science and Practice of Pharmacy,* Limmer, D., Ed.; Lippincott: Baltimore, 2000, 894-902.

Rauwendaal, C. *Polymer Extrusion*, 3rd Ed.; Hanser: New York, 1994; 15-48.

Repka, M.A.; Gerding, T.G.; Repka, S.L.; McGinity, J.W. Influence of plasticizers and drugs on the physical-mechanical properties of hydroxypropylcellulose films prepared by hot-melt extrusion. Drug Development and Industrial Pharmacy.1999, 25, 625–633.

Repka, M.A.; McGinity, J.W. Physical-mechanical, moisture absorption and bioadhesive properties of hydroxypropylcellulose hot-melt extruded films. Biomaterials. 2000, 21, 1509-1517.

Repka, M.A.; Repka, S.L.; McGinity, J.W. Bioadhesive hot-melt extruded film for topical and mucosal adhesion applications and drug delivery and process for preparation thereof.. US Patent 6,375,963, 2002.

Reynolds, A.D. A new technique for the production of spherical particles. Manufacturing Chemist and Aerosol News. 1970, 41, 40-43.

Ritschel, W.A. Pharmacokinetic and biopharmaceutical aspects in drug delivery. In: Tyle, P. (Ed.), Drug Delivery Devices: Fundamentals and Applications. Marcel Dekker, New York, 1988, 19–79.

Ritschel, W.A., Biopharmaceutic and pharmacokinetic aspects in the design of controlled release peroral drug delivery systems. Drug Development and Industrial Pharmacy. 1989, 15, 1073–1103.

Sandberg, A.; Blomqvist, I.; Jonsson, U.; Lundborg, P. Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol: a comparison with conventional tablets. European Journal of Clinical Pharmacology. 1988, 33 (Suppl.), S9–S14.

Sato, H.; Miyagawa, Y.; Okabe, T.; Miyajima, M.; Sunada, H., Dissolution mechanism of diclofenac sodium from wax matrix granules. Journal of Pharmaceutical Sciences. 1997, 86(8), 929-934.

Schæfer, T.; Mathiesen, C. Melt pelletization in a high shear mixer. IX. Effects of binder particle size. International Journal of Pharmaceutics. 1996, 139, 139–148.

Sears, J.K.; Darby, J.R. *The Technology of Plasticizer*. John Wiley & Sons: New York, 1982.

Seo, A.; Schæfer, T. Melt agglomeration with polyethylene glycol beads at a low impeller speed in a high shear mixer. European Journal of Biopharmaceutics. 2001, 52, 315–325.

Sood, A.; Panchagnula, R. Design of controlled release delivery systems using a modified pharmacokinetic approach: a case study for drugs having a short elimination half-life and a narrow therapeutic index. International Journal of Pharmaceutics. 2003, 261 (1-2), 27-41.

Sprockel, O.L.; Sen, M.; Shivanand, P.; Prapaitrakul, W. A melt-extrusion process for manufacturing matrix drug delivery systems. International Journal of Pharmaceutics. 1997, 155, 191-199.

Wan, L.; Heng, P.; Ling, B.L.; Effect of polyvinylpyrrolidone solutions containing dissolved drug on characteristics of lactose fluidized bed granules. International Journal of Pharmaceutics. 141 (1-2), 1996, 161-170.

Wu, C.; McGinity, J.W. Non-traditional plasticization of polymeric films. International Journal of Pharmaceutics. 1999, 177, 15–27.

Zhang, F.; McGinity, J.W. Properties of sustained release tablets prepared by hot-melt extrusion. Pharmaceutical Development and Technology. 1999, 4, 241–250.

Zhang, F.; McGinity, J.W. Properties of hot-melt-extruded theophylline tablets containing poly(vinyl acetate). Drug Development and Industrial Pharmacy. 2000, 26, 931-942.

Zhang, Y.; Zhang, Z.; Wu, F. A novel pulsed-release system based on swelling and osmotic pumping mechanism. Journal of Controlled Release. 2003, 89 (1), 47-55.

Zhu, Y.; Shah, N.H.; Malick, A.W.; Infeld, M.H.; McGinity, J.W. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. International Journal of Pharmaceutics, 2002, 241(2), 301-310.

Table 1.1: Polymers that have been used as carriers in pharmaceutical melt-extrusion applications.

CHEMICAL NAME	TRADE NAME
Ammonio methacrylate copolymer	Eudragit® RS/RL
Poly(dimethylaminoethylmethacrylate-co-methacrylic esters)	Eudragit® E
Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid)	Eudragit® 4135F
Poly(methacrylic acid-co-methyl methacrylate) 1:2	Eudragit® S
Hydroxypropyl cellulose	Klucel®
Ethyl cellulose	Ethocel®
Cellulose acetate butyrate	CAB 381-0.5
Cellulose Acetate Phthalate	--
Poly(ethylene oxide)	Polyox® WSR
Poly(ethylene glycol)	Carbowax®
Poly(vinyl pyrrolidone)	Kollidon®
Poly(vinyl acetate)	Sentry® plus
Hydroxypropyl Methylcellulose Phthalate	--
Polyvinylpyrrolidone-co-vinyl acetate	Kollidon® VA64
Hydroxypropyl Methylcellulose	Methocel®
Hydroxypropyl Methylcellulose Acetate Succinate	Aqoat-AS®
Poly(lactide-co-glycolide)	PLGA
Polyvinyl Alcohol	Elvanol®
Chitosan Lactate	Sea-Cure®

Table 1.1: Continued.

CHEMICAL NAME	TRADE NAME
Pectin	Obipektin®
Carbomer	Carbopol® 974P
Polycarbophil	Noveon® AA-1
Poly(ethylene-co-vinyl acetate)	Elvax® 40W
Polyethylene	--
Poly(vinyl acetate-co-methacrylic acid)	CIBA-I
Epoxy resin containing secondary amine	CIBA HI
Polycaprolactone	--
Carnauba Wax	--
Ethylene-vinyl acetate copolymer	Evatane®
Glyceryl Palmitostearate	Precirol® ATO 5
Hydrogenated Castor & Soybean Oil	Sterotex® K
Microcrystalline Wax	Lunacera®
	Paracera®
Corn Starch	--
Maltodextrin	--
Pregelatinized Starch	--
Isomalt	Palatinit®
Potato Starch	--
Citric Acid	--
Sodium Bicarbonate	--

Table 1.2: Analytical methods used to study the morphology of solid dispersions.

Hot stage microscopy
Powder X-ray diffraction
Thermal analysis/Differential scanning calorimetry
Near infrared spectroscopy
Microcalorimetry

Figure 1.1: Vertical, single screw extruder (Randcastle RCP-750 Microtruder).

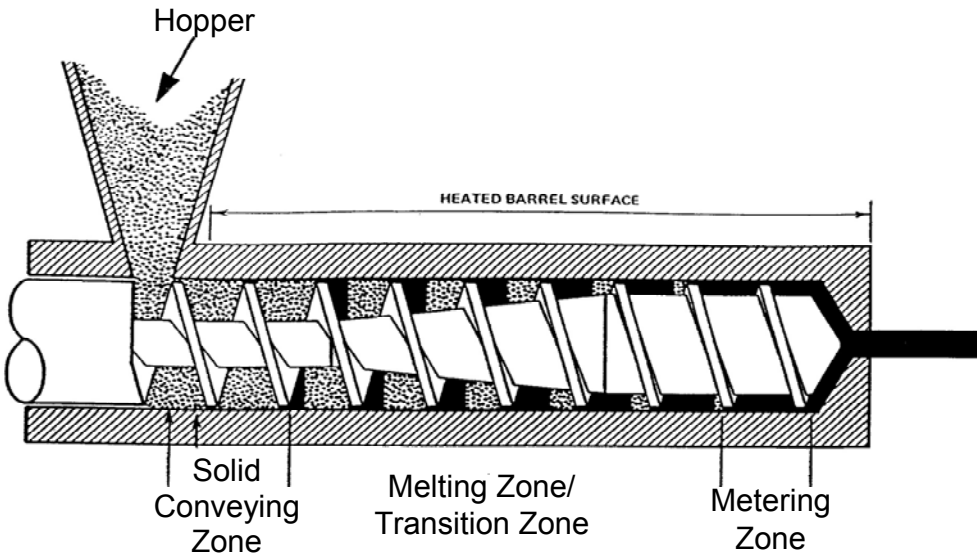
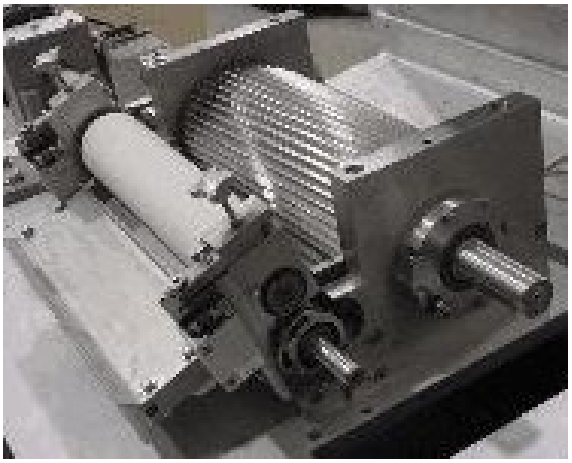


Figure 1.2: Screw design of conventional single screw extruder.

A.



B.

Figure 1.3: Pelletizers used in melt-extrusion applications.

Key: A. Strand pelletizer; B. Die face pelletizer.

Chapter 2: Production of spherical pellets by a novel hot-melt extrusion and spheronization process

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2.1 INTRODUCTION

The aim of controlled-release technology is to achieve a predictable and reproducible drug release rate over an extended period of time. Controlled-release delivery systems allow reduced dosing frequency and provide constant drug levels in the blood, thus increasing patient compliance and decreasing adverse drug events (Berner 1992). Pellets are frequently used in controlled-release systems because they are freely dispersed in the gastrointestinal tract and they offer flexibility for further modification. Wet-mass extrusion and spheronization is the more established method of producing spherical pellets, but pellets manufactured by this method are usually film-coated to control drug release. Researchers have investigated matrix systems produced by extrusion and spheronization to control drug release and to avoid difficulties associated with film-coating, but many of these systems only offer limited control of drug release or present processing difficulties (Gandhi 1999).

Hot-melt extruded dosage forms are complex mixtures of the active ingredient, matrix carrier(s) and functional excipients. These excipients are broadly classified as release-modifying agents, bulking agents, processing agents and miscellaneous additives. The selection and use of various excipients can

impart specific properties to melt-extruded pharmaceuticals in a manner similar to those in traditional dosage forms (Zheng 1999; Repka 2000).

The purpose of this investigation was to characterize a hot-melt extrusion (HME) process to manufacture spherical pellets and to examine the controlled drug release properties of the spherical pellets produced by the novel thermal process.

2.2 MATERIALS AND METHODS

2.2.1 Materials

Eudragit® Preparation 4135 F (4135 F) is an acrylic polymer that was donated by Röhm GmbH (Darmstadt, Germany). Anhydrous theophylline USP/NF was purchased from Spectrum Quality Products, Inc. (Gardena, CA). Poly(ethylene glycol) 8000 powder (PEG 8000, NF) was supplied by Dow Chemical (Midland, MI), and microcrystalline cellulose (MCC) was provided by FMC (Newark, Delaware).

2.2.2 Spherical pellet production

The pellet formulation for melt-processing consisted of the thermal carrier, 4135 F (48%), anhydrous theophylline (30%) as the model drug, and functional excipients including PEG 8000 (7%) and MCC (15%). Eudragit® Preparation 4135 F was first ground using a cryogenic grinder since it was supplied as large granules. The powders were passed through a 30-mesh (600 μm) screen and the powder formulation was blended for 5 min at 2000 revolutions per min (rpm) in a high-shear granulator (Robot Coupe® RSI 3VG; Ridgeland, MS) to assure adequate mixing.

The dry powder blend was extruded using a Randcastle Microtruder® RCP-0750 (Cedar Grove, NJ) vertical, single-screw extruder. The extruder temperature controllers were set as follows: Zone 1 = 82°C, Zone 2 = 118°C, Zone 3 = 121°C and Die = 121°C. The formulation was fed into the hopper after the extruder zones and die had equilibrated to the set temperatures. After exiting the cylindrical die, the polymeric strand with a diameter of 1.22 ± 0.03 mm was fed into a Randcastle Pelletizer RCP-2.0 and was uniformly cut into cylindrical pellets 1.22 ± 0.04 mm in length. The pellets were allowed to cool to room temperature under ambient conditions and then a 75 g sample was transferred into a Caleva Model 120 Spheronizer (Dorset, England). A Milwaukee™ Model 1220 (International Tool Corporation; Davie, FL) heat gun was used to facilitate pellet deformation by circulating hot air through the product exit of the spheronizer. The pellets were marumerized for approximately 45 min at 65-70°C and dusted with microcrystalline cellulose to prevent agglomeration during processing. The HME pellets exhibited a 1.6% w/w loss on drying after lyophilization for 72 h. The spheronized pellets were packaged in sealed HDPE bottles and stored at 25°C/60% RH and 40°C/75% RH. A schematic representation of the HME and spheronization process is shown in Figure 2.1.

2.2.3 Thermal analysis of formulation components and pellets

Thermal gravimetric analysis (TGA) of pellet formulation components was performed with a Perkin Elmer TGA 7 using a heating rate of 10°C/min from 50°C to 600°C. The polymer glass transition temperatures (*Tg*) were determined by modulated differential scanning calorimetry (MDSC, TA Instruments Model 2920; New Castle, DE) using a heating rate of 5°C/min over a temperature range of –20°C to 120°C.

2.2.4 Pellet morphology

The morphology of gold:palladium (60:40, Ted Bench Top Sputter Coater) coated HME pellets were examined using a Philips Model 515 Scanning Electron Microscope (SEM).

2.2.5 Dissolution

Dissolution testing of the theophylline containing pellets was conducted using the USP 27 Apparatus 2 (paddle method, VanKel VK6010; Cary, NC) in 900 mL of medium maintained at 37°C and 100 rpm. The pH 1.0 medium was 0.1 N HCl, and the pH 3.0, 6.8 and 7.4 media were 50 mM phosphate buffer solutions. A VanKel VK8000 auto sampler was used to withdraw 4 mL samples at 0.25, 0.5, 1, 2, 4, 6 and 12 h time points. Filtered samples were assayed by UV spectrophotometry (DU-65, Beckman Instruments; Fullerton, CA) at 272 nm. Dissolution tests were performed in triplicate.

2.3 RESULTS

Eudragit® Preparation 4135 F is an experimental copolymer composed of methyl acrylate, methacrylic acid and methyl methacrylate. The preparation is ideal for colonic delivery systems since it is soluble in aqueous media at pH 7.0 and above. The copolymer is also an excellent candidate for thermal processing since it is flexible and has a low *Tg* of 49.2°C as experimentally determined by MDSC.

A powder formulation composed of theophylline and 4135 F with functional excipients was melt-extruded and spheronized. Functional excipients in melt-extruded powder blends may be classified as release-modifying agents, bulking agents, processing agents and miscellaneous additives. MCC was chosen

as a thermal processing aid for the powder blend used in this study since it acted as an anti-tacking agent. PEG 8000 was included in the formulation to facilitate HME since it plasticized the 4135 F. The presence of a solid-state plasticizer of the acrylic polymer lowered the *Tg* of the polymer preparation, which allowed for lower processing temperatures and shorter processing times. Although the experimentally determined *Tg* of 4135 F was 49.2°C, the experimentally determined *Tg* of the plasticized HME product was 23.1°C. Furthermore, TGA demonstrated that the formulation was suitable for HME since the formulation components did not experience weight loss at the processing temperatures as illustrated in Figure 2.2.

The SEM micrographs displayed in Figure 2.3 demonstrate the differences in the surface morphologies of the beads as a function of spheronization time. The HME bead manufactured using a 45 min spheronization time exhibits a surface indentation (2.3 A). The indentation on either side of the pellet represents the cut edges of the unspheronized pellet. Spheronization rounds the pellet ends, thus increasing spheronization time can reduce or eliminate the indentation. The spherical pellet in Figure 2.3 B illustrates the elimination of the surface indentation with an 80 min spheronization time. However, dissolution investigations found no difference between the drug release rates from pellets with different spheronization times.

The melt-extruded and spheronized matrix pellets exhibited control of theophylline release as a function of medium pH. The theophylline release profiles in pH 1.0 and 3.0 media are similar with both releasing approximately 52% of the drug after 12 h (Figure 2.4). The drug release profiles of the HME beads were characteristic of a diffusion-controlled matrix system. Drug release

was governed by solute diffusion within the matrix phase and decreased with time due to a receding drug boundary and to a decreasing area at the diffusion front. Researchers have noted that matrix systems exhibit negligible or no movement of the diffusion front due to swelling or erosion when the matrix polymer is insoluble in the dissolution medium (Lee 1992). The matrix polymer, 4135 F, of the studied HME beads was insoluble in the acidic aqueous media. Additionally, Follonier and coworkers noted that porosity is an important determinant of drug release from melt-extruded sustained release pellets (Follonier 1994; Follonier 1995). Slowed drug release rates from HME beads is further explained by decreased free volume since thermal treatment at elevated pressures decreases polymer free volume in the bead. Free volume is defined as the volume of an amorphous material that is not occupied by molecules of the amorphous material. Available free volume in an amorphous material determines diffusion of other molecules through the matrix material, thus increased degree of packing results in decreased drug release rates (Wicks 1986). When the HME spherical pellets were tested in pH 6.8 medium, approximately 69% of the theophylline was released after 12 h (Figure 2.4). Theophylline release increased in pH 6.8 medium because it was close to the pH at which the polymer starts to dissolve. Complete theophylline release was attained in approximately 4 h when the HME beads were tested in pH 7.4 medium. Drug release behavior in pH 6.8 and 7.4 was diffusion-controlled, but polymer swelling and dissolution also influenced drug release. The early stage of the dissolution process is dominated by polymer swelling as the polymer changes from a glassy to a rubbery state due to water penetration and subsequent plasticization. Dissolution of the polymer occurs when the water concentration at the polymer surface exceeds a critical

concentration of macromolecular disentanglement (Lee 1992). HME beads remained intact after dissolution testing for 12 h in pH 1.0, 3.0 and 6.8 media. The matrix beads did not disintegrate in these media due to matrix polymer insolubility and to significant polymer chain entanglement in the core matrix. The HME beads completely dissolved after dissolution testing for approximately 4 h at pH 7.4, where the matrix polymer was soluble.

Although the *Tg* of the HME product was 23.1°C as determined by MDSC, the pellets exhibited no sticking after storage for 1 week in sealed HPDE containers at 40°C/75% RH. Furthermore, theophylline release properties of the HME beads did not change after storage for 1 year in sealed HDPE containers at 25°C/60% RH as demonstrated in Figure 2.5.

2.4 DISCUSSION

The findings from this study demonstrated that controlled-release spherical matrix pellets could be successfully prepared using a HME and spheronization process. Melt-extruded matrix pellets exhibited diffusion-controlled drug release. Drug release from the acrylic matrix system studied was influenced by the pH of the dissolution medium since the solubility of the matrix polymer, Eudragit® Preparation 4135 F, is pH dependent.

HME pellets are a unique dosage form because they can be used for immediate release or controlled-release applications depending on the properties of the matrix polymer. Conventional pellets must be coated to prevent rapid drug release, even when an insoluble matrix is employed. HME pellets do not require film-coating to control drug release, but they can be film-coated to further modify drug release in the gastrointestinal tract. Although our study employed Eudragit® Preparation 4135 F to produce spherical pellets, other polymers and

thermal agents are currently under investigation to demonstrate the versatility of this melt-extrusion and spheronization process.

2.5 REFERENCES

Aitken-Nichol, C.; Zheng, F.; McGinity, J.W. Hot-melt extrusion of acrylic films. Pharmaceutical Research. 1996, 13, 804–808.

Berner, B.; Dinh, S. Fundamental concepts in controlled-release. In *Treatise on Controlled Drug Delivery*, Kydonieus, A., Ed.; Marcel Dekker: New York, 1992; 155-195.

Follonier, N.; Doelker, E.; Cole, E.T. Evaluation of hot-melt extrusion as a new technique for the production of polymer based pellets for sustained release capsules containing high loading of freely soluble drugs. Drug Development and Industrial Pharmacy. 1994, 20, 1323–1339.

Follonier, N.; Doelker, E.; Cole, E.T. Various ways of modulating the release of diltiazem hydrochloride from hot–melt extruded sustained release pellets prepared using polymeric materials. Journal of Controlled Release. 1995, 36, 243–250.

Gandhi, R.; Kaul, C.L.; Panchagnula, R. Extrusion and spheronization in the development of oral controlled-release dosage forms. Pharmaceutical Science and Technology Today. 1999, 2, 160-170.

Lee, P.I. Diffusion-controlled matrix systems. In *Treatise on Controlled Drug Delivery*, Kydonieus, A., Ed.; Marcel Dekker: New York, 1992; 155-195.

McGinity, J.W.; Koleng, J.J.; Repka, M.A.; Zhang, F. Hot-melt extrusion technology. In *Encyclopedia of Pharmaceutical Technology*, 2nd Ed.; Swarbrick, J.; Boilan, J.C., Eds.; Marcel Dekker: New York, 2000; Vol. 19, 2nd ed., Dekker, New York, 2000; 203-226.

Repka, M.A.; Gerding, T.G.; Repka, S.L.; McGinity, J.W. Influence of plasticizers and drugs on the physical-mechanical properties of hydroxypropylcellulose films prepared by hot-melt extrusion. Drug Development and Industrial Pharmacy. 1999, 25, 625–633.

Repka, M.A.; McGinity, J.W. Physical-mechanical, moisture absorption and bioadhesive properties of hydroxypropylcellulose hot-melt extruded films. Biomaterials. 2000, 21, 1509-1517.

Wicks, Z.W. Free volume and coatings formulator. Journal of Coating Technology. 1986, 58, 23-32.

Zheng, F.; McGinity, J.W. Properties of sustained release tablets prepared by hot-melt extrusion. Pharmaceutical Development and Technology. 1999, 4, 241-250.

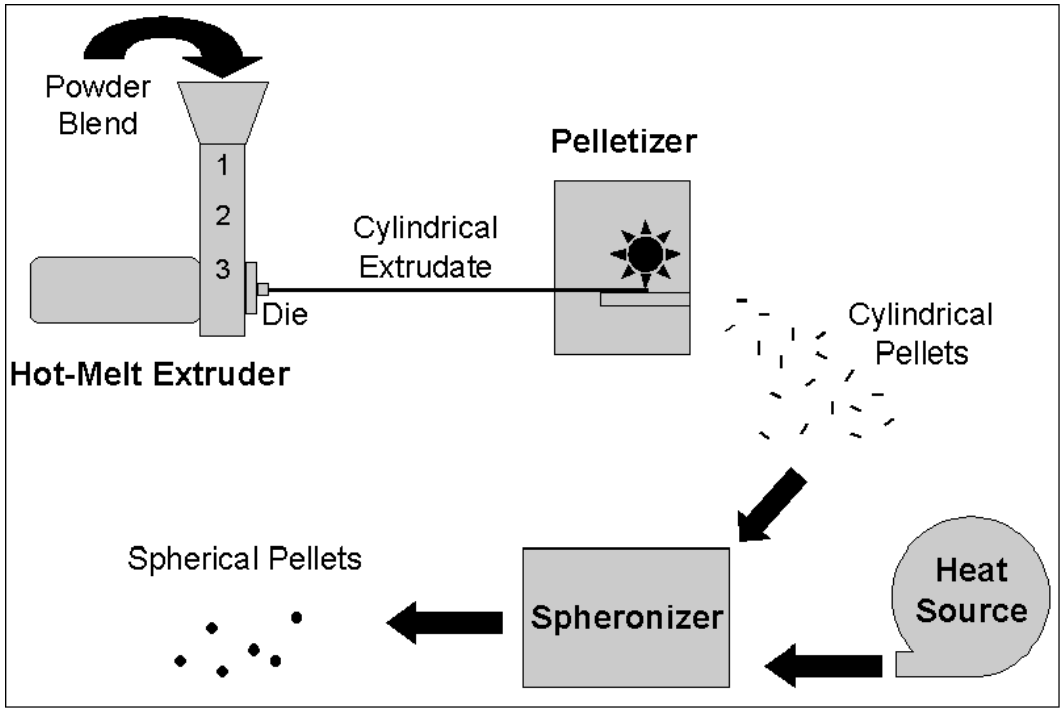


Figure 2.1: Diagram of the HME and spheronization process.

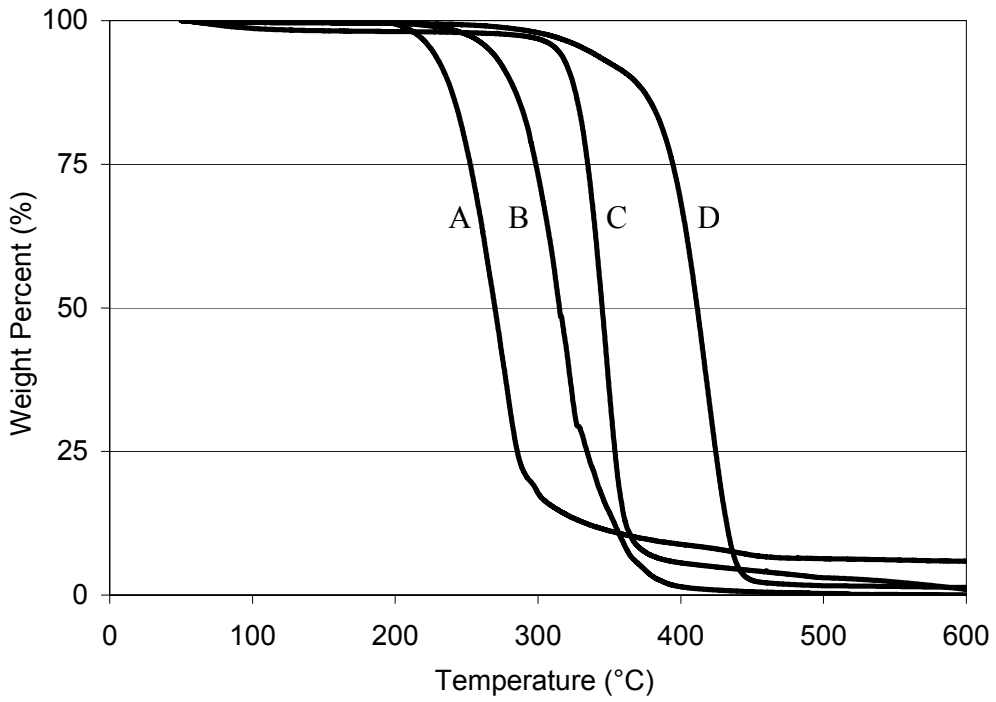
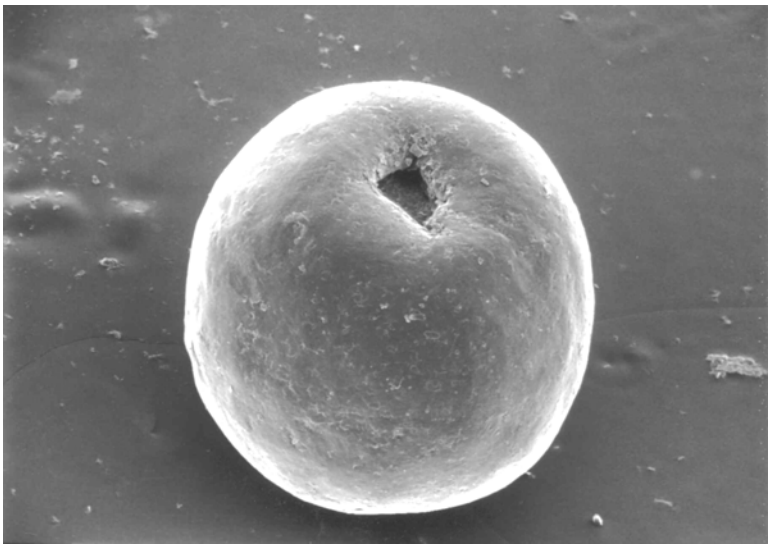


Figure 2.2: Thermal gravimetric analysis of pellet formulation components.

Key: A. PEG 8000; B. Theophylline; C. Microcrystalline Cellulose; D. Eudragit® Preparation 4135 F.

A.



B.

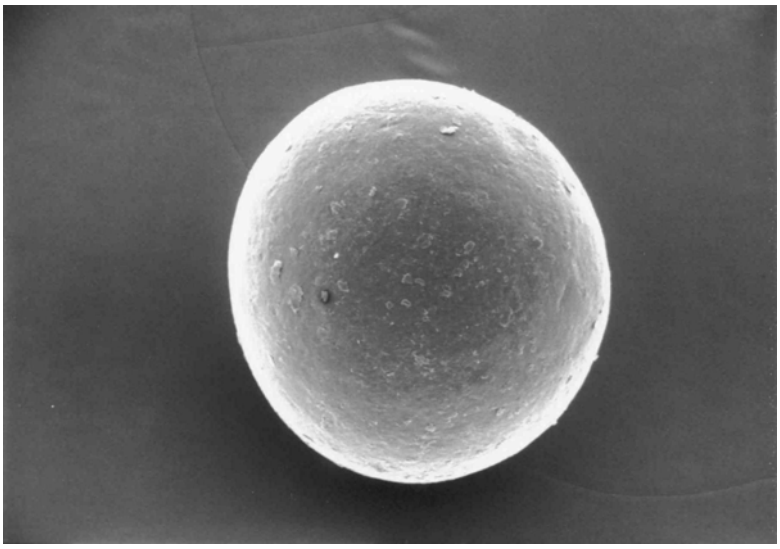


Figure 2.3: SEM micrographs of spherical pellets (approximately 1.2 mm diameter).

Key: A. Spherical pellet produced by HME after spheronization for 45 min; B. Spherical pellet produced by HME after spheronization for 80 min.

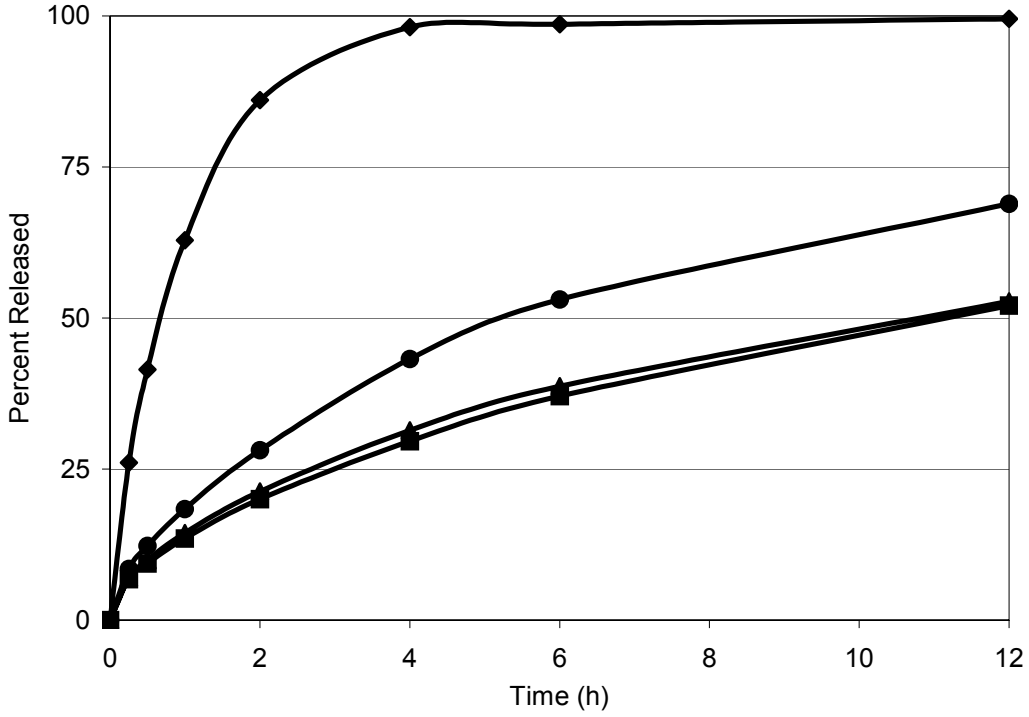


Figure 2.4: Influence of medium pH on the release of theophylline from pellets produced by HME and spheronization (USP 27 Apparatus 2, 900 mL, 37°C, 100 rpm, $n = 3$).

Key: ▲ pH 1.0; ■ pH 3.0; ● pH 6.8; ◆ pH 7.4.

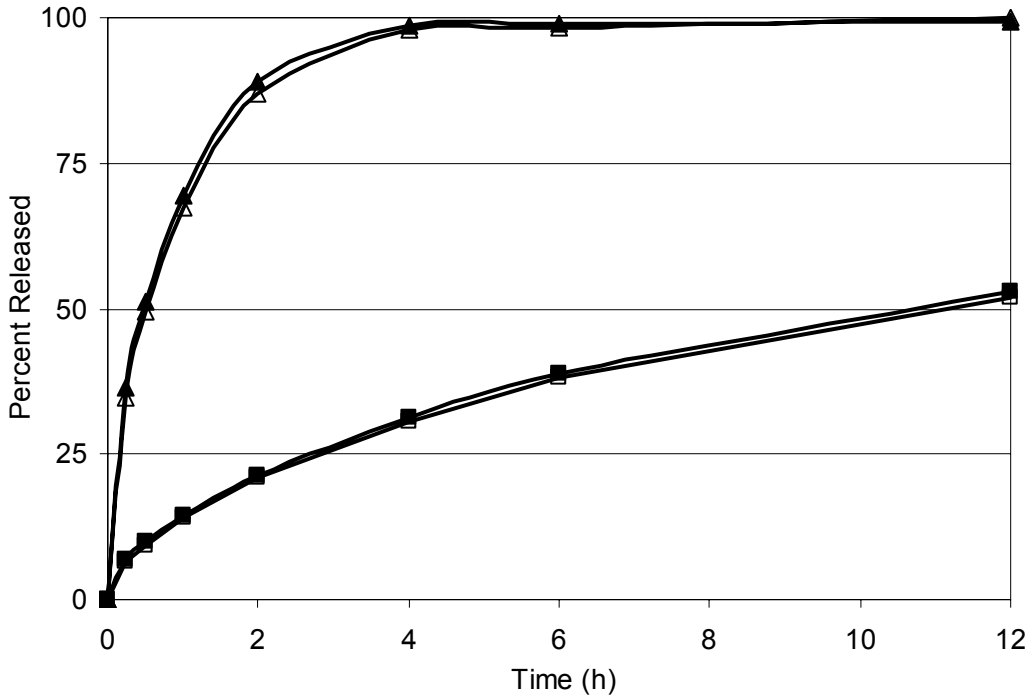


Figure 2.5: Effect of 1 year storage at 25°C/60% RH on the release of theophylline from hot-melt extruded and spheronized pellets (USP 27 Apparatus 2, 900 mL, 37°C, 100 rpm, $n = 3$).

Key: ▲ Initial, pH 1.0; △ Stored, pH 1.0; ■ Initial, pH 7.4; □ Stored, pH 7.4.

Chapter 3: Properties of drug-containing spherical pellets produced by a hot-melt extrusion and spheronization process

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3.1 INTRODUCTION

Recent advances in controlled-release technology have allowed the development of drug delivery systems that permit less frequent dosing and provide constant blood levels of active pharmaceutical ingredients (API). Controlled-release dosage forms increase patient compliance and minimize adverse drug events (Berner 1992). Although there are significant formulation differences among various controlled-release dosage forms, these preparations can be broadly categorized as either single or multiple unit systems.

Multiple unit dosage forms such as pellets offer advantages as constituents of controlled-release systems. Pellets are rapidly and evenly dispersed in the gastrointestinal tract upon oral administration, thus maximizing drug absorption and reducing inter- and intra-subject variability due to differences in gastric emptying rates (Vergote 2001). Furthermore, pellets offer flexibility for further modification, such as film-coating or compression into multiparticulate tablets. Betageri et al. (1995) described methods of manufacturing controlled-release pellets, which included coating drug-containing pellets with a polymer or placing the drug in an insoluble or eroding bead matrix.

Many researchers have demonstrated the effectiveness of film-coating in controlling drug release (Porter 2000). Although film-coating is a conventional method of producing controlled-release pellets, the process is not without problems. This technique is labor intensive and costly since coating systems require water or solvent removal, which may include a post-coating drying or curing step at elevated temperatures. Additionally, drug release profiles may not be reproducible due to variations in film-coating thickness (Andersson 2000) or imperfections in the coating that result from aging or cracking of the polymer film (Lippold 2001). Employing matrix pellet systems to control drug release may circumvent problems associated with film-coating (Gandhi 1999). Cold-mass extrusion and spheronization techniques have been used to produce controlled-release matrix pellets, which utilize an eroding matrix system or release retarding agents. Mehta and coworkers (2001) manufactured eroding matrix pellets using the acrylic polymers Eudragit® L 100-55 and Eudragit® S 100. Controlled-release pellets have also been produced using release-modifying agents such as hydrophobic components (Ghali 1989), cellulose-derivatives (Levis 2001), chitosan (Goskonda 1993) and pH adjusters (Bianchini 1992).

Nevertheless, many of these systems offer limited control of drug release or present processing difficulties. Additionally, cold-mass extrusion and spheronization methods generally utilize water and require an energy demanding and time consuming drying phase. Earlier reports have also demonstrated that drug release rates from matrix systems depend significantly on the processing technique and that matrix systems developed using thermal methods display slower drug release rates than systems produced by non-thermal methods (Onay-Basaran 1985, Billa 1998).

Hot-melt extrusion (HME) is a thermal processing method that offers advantages over conventional granulation methods since molten binders are employed instead of water. HME generates a product of uniform shape by forcing materials through a die under controlled conditions. HME is an efficient, continuous and solvent-free process (Liu 2001) that has been applied in the pharmaceutical field to prepare granules, sustained-release tablets and transdermal drug delivery systems (Follonier 1994, Aitkin-Nichol 1999, Repka 1999, Zhang 1999, Zhang 2000). Furthermore, intense mixing and agitation during HME processing cause suspended drug particles to deaggregate in the polymer melt, resulting in a more uniform dispersion of fine particles (McGinity 2000).

Thus, a melt-extrusion process would offer advantages as a method for spherical pellet production. The objectives of the present study were to investigate physical characteristics of pellets produced by either wet-mass extrusion or HME and to study the mechanisms of drug release from matrix pellets. Properties investigated included particle size distribution, morphology, porosity and dissolution characteristics.

3.2 MATERIALS AND METHODS

3.2.1 Materials

Eudragit® Preparation 4135 F (4135 F) was donated by Röhm GmbH (Darmstadt, Germany). Anhydrous theophylline USP/NF was purchased from Spectrum Quality Products, Inc. (Gardena, CA). Poly(ethylene glycol) 8000 (PEG 8000, Carbowax® 8000) powder was supplied by Dow Chemical (Midland, MI), and microcrystalline cellulose (MCC, Avicel® PH-101) was donated by

FMC (Newark, Delaware). All materials were used as received from the supplier except where noted.

3.2.2 Spherical pellet production

The pellet formulation consisted of the polymer 4135 F (48%), theophylline (30%), polyethylene glycol 8000 (7%) and microcrystalline cellulose (15%). Eudragit® Preparation 4135 F was received as granules, but polymer particle size was reduced to a fine powder using a Micron Powder System model CF cryogenic grinder (Summit, NJ). Formulation components were passed though a 30-mesh (600 μm) screen and then blended for 5 min at 2000 revolutions per min (rpm) in a Robot Coupe® RSI 3VG high-shear granulator (Ridgeland, MS). The powder blend was then processed by either wet-mass extrusion and spheronization or HME and spheronization.

For the sample processed by conventional wet-mass extrusion and spheronization, approximately 15% w/w water was added to the dry powder blend before the damp mass was cold-mass extruded using a LCI bench top granulator (Tokyo, Japan) equipped with a 1.0 mm screen. The extruded granules were transferred into a Caleva 120 spheronizer (Dorset, England) and spheronized for 2.5 min. The pellets were dried at 25°C/60% RH for 24 h, and the 14-16-mesh size (1.40-1.18 mm) fraction was collected for further testing.

For the sample processed by HME, the powder blend was extruded using a Randcastle Microtruder® RCP-0750 (Cedar Grove, NJ) single-screw extruder. The extruder temperature controllers were set as follows: Zone 1 = 82°C, Zone 2 = 118°C, Zone 3 = 121°C and Die = 121°C. A cylindrical die 1.2 mm in diameter was used. After exiting the die, the polymeric strand, exhibiting a diameter of 1.22 ± 0.03 mm, was fed into a Randcastle RCP-2.0 pelletizer and uniformly cut

into cylindrical pellets 1.22 ± 0.04 mm in length. The pellets were cooled to ambient temperature, and a 75 g sample was transferred into a Caleva Model 120 spheronizer. A Milwaukee™ Model 1220 (International Tool Corporation; Davie, FL) heat gun was used to control the temperature of the spheronizer bowl at 60-70°C since the pellets did not deform when spheronized at ambient temperature. The pellets were spheronized for 45 min, and the 14-16-mesh size (1.40-1.18 mm) fraction was collected for further testing.

3.2.3 Pellet morphology and particle size distribution

The surface and cross-sectional morphologies of spherical pellets produced by wet-mass extrusion and HME were examined using a Hitachi S-4500 field emission scanning electron microscope (Rolling Meadows, IL). The particle size distribution of a 200 g sample was determined by shaking for 15 min with USA standard testing sieves (Arthur H. Thomas Company; Philadelphia, PA).

3.2.4 Thermal analysis of pellets

The thermal properties of Eudragit® Preparation 4135 F and the processed pellets were characterized using modulated differential scanning calorimetry (MDSC, Model 2920, TA Instruments, New Castle, DE). Samples of approximately 10 mg were accurately weighed and hermetically sealed in aluminum pans. The samples were analyzed under a nitrogen atmosphere at a heating rate of 3°C per min over the temperature range of –20°C to 120°C. Modulation was set at +/- 1°C every 60 s. The reported glass transition temperature (*Tg*) was the midpoint of the integrated first heating cycle transition. MDSC analysis of samples was performed in triplicate.

3.2.5 Dissolution

Dissolution testing of the theophylline-containing pellets was conducted using the USP 27 Apparatus 2 dissolution method (Paddle Method, VanKel VK6010; Cary, NC) in 900 mL of media maintained at 37°C with a paddle agitation rate of 100 rpm. The pH 1.0 medium was 0.1 N HCl, while the pH 3.0, 6.8 and 7.4 media were 50 mM phosphate buffered solutions. A VanKel VK8000 auto sampler was used to withdraw 4 mL samples at 0.25, 0.5, 1, 2, 4, 6 and 12 h time points.

In addition to conventional dissolution studies, USP 27 Apparatus 3 dissolution testing (Reciprocating Cylinder Method, VanKel Bio-Dis II; Cary, NC) was performed in 250 mL of media at 37°C and 20 dips per min (dpm). The media evaluated included pH 1.0 (0.1 N HCl), 3.0, 5.0, 6.8 and 7.4 (50 mM phosphate buffer). The theophylline-containing beads transited though multiple media, including 2 h in pH 1.0, 1 h in pH 3.0, 5.0 and 6.8, and 3 h in pH 7.4. Apparatus 1 and 2 dissolution tests were performed in triplicate, and complete drug release was determined after the final sample time point by high-speed agitation of the dissolution vessel contents for 2.5 min with a Polytron® homogenizer (Brinkmann Instruments; Westbury, NY). Filtered dissolution samples were assayed by UV spectrophotometry at 272 nm.

3.2.6 X-ray diffraction

Powder X-ray diffraction profiles of formulation components and HME pellets were obtained using a Philips PW 170 X-ray generator equipped with a PW 1710 X-ray diffractometer. The operating current and voltage were 40 mA

and 40 kV, respectively. Samples were examined using a 2-theta scanning range from 5° to 50° at a scanning rate of 2° per min.

3.2.7 Porosity

Pellet porosity measurements were calculated using equation 3.1 for percent effective porosity (Varner 1991, Andreola 2000):

$$\%\varepsilon = [(\rho_t - \rho_b) / \rho_b] \text{ x } 100 \qquad \text{(Eq. 3.1)}$$

where ε = effective porosity, ρ_t = true density and ρ_b = bulk density. The true density of the powder formulation was determined in triplicate using He pycnometry (Micrometrics® AccuPyc 1330 pycnometer; Norcross, GA) to measure the density of the powder formulation prior to processing. Hg porosimetry (Micrometrics® PoreSizer 9320; Norcross, GA) was employed to determine the bulk densities of spherical pellets, in triplicate, after processing. Water was removed from powders and pellets by lyophilization for 72 h prior to density determinations.

3.3 RESULTS AND DISCUSSION

The current study used thermal processing to prepare pellets containing Eudragit® Preparation 4135 F, an experimental copolymer composed of methyl acrylate, methacrylic acid and methyl methacrylate. This material has potential applications for colonic delivery systems since the polymer is soluble in aqueous media at pH 7.0 and above. Eudragit® Preparation 4135 F is flexible and has a low glass transition temperature (*Tg*), making this material an excellent candidate for thermal processing.

A powder blend containing theophylline, 4135 F, MCC and PEG 8000 was melt-extruded and then spheronized. MCC was included in the formulation as a massing aid during cold-mass extrusion and as an anti-tacking agent during thermal processing. PEG 8000 was included as a plasticizer to facilitate HME processing. The presence of a solid-state plasticizer further lowered the *Tg* of the acrylic polymer preparation, which allowed for lower processing temperatures and shorter processing times. Reduction of these parameters diminishes the propensity for degradation of thermally labile components (Repka 1999). The experimentally determined *Tg* of 4135 F was 50.3 ± 0.5°C, whereas the *Tg* of the plasticized, melt-extruded product was 24.8 ± 1.3°C.

The SEM micrographs in Figure 3.1 illustrate the morphological features of bead surfaces at low magnification. The HME bead (3.1 B) exhibited a surface indentation, although no granular characteristics were observed as noted with beads produced by wet-mass extrusion (3.1 A). The indentation on the HME bead represents the cut surface of the unspheronized granule. Melt-extruded pellets were spheronized for 45 min, and pellet surface morphology was visually examined at 5 min intervals. The surface indentation was reduced or eliminated with increasing spheronization time. Dissolution studies found no difference between the drug release rates from pellets after spheronization for 5 min. A significant advantage of spherical pellets is in film-coating and compression applications.

The particle size distributions of beads produced by wet-mass extrusion and HME are represented in Figure 3.2. The mesh size number indicates the screen opening size, which decreases as the mesh size number increases. Approximately 90% of the HME beads were of size 14-16-mesh (1.40-1.18 mm),

while only 50% of the wet-mass extruded beads were in this size range. Thus, HME processing yielded a narrower particle size distribution since HME pellet particle size is a function of spherical orifice diameter of the extruder die and the rate of pelletization. Production of beads with a narrow particle size distribution is desired for controlled-release products (Wheatley 1997, Chopra 2002) and for applications such a film-coating (Rubio 1994).

The HME beads exhibited controlled theophylline release in all dissolution media tested with the exception of pH 7.4, while the wet-mass extruded beads exhibited rapid release in all dissolution media studied. As seen in Figure 3.3, wet-mass beads exhibited complete theophylline dissolution after approximately 4 h in pH 1.0 medium, whereas only 52% drug release was observed after 12 h in the same medium for HME beads. The dissolution profiles of wet-mass extruded and HME pellets in pH 1.0, 3.0, 6.8 and 7.4 media are summarized in Table 3.1 as the time point when at least 50% theophylline was released. Dissolution results for HME pellets in pH 1.0 and 3.0 media were similar, but a faster theophylline release rate was observed in buffered medium pH 6.8. The drug release rate from the HME pellets increased in this medium since the pH was near 7.0, the value at which the polymer is soluble. The dissolution results indicate that both wet-mass extruded and HME exhibited rapid drug release in pH 7.4 medium.

Higuchi (1961) developed a mathematical model for the release properties of ointment bases containing drugs in suspension. In 1963, Higuchi used this equation to explain the release properties of solid drug particles dispersed in solid matrices. The theoretical analysis considered the mechanism of drug release from both homogeneous and heterogeneous solid matrix systems.

Drug release from a homogenous matrix is due to medicament diffusion through the enveloping matrix, whereas release from a heterogeneous or granular matrix is the result of drug leaching as dissolution medium penetrates the matrix through pores, cracks and intragranular spaces. The Higuchi model describes drug release from planar systems, where the percentage of drug released is proportional to the square root of time. An equation was later derived by Baker and Lonsdale that is based on the Higuchi model, but describes drug diffusion from a spherical matrix. This equation has been used to model release data from several formulations of microcapsules and microspheres (Costa 2001, Zhang 1999):

$$(3/2)[1 - (1 - (M_t/M_\infty))^{2/3}] - (M_t/M_\infty) = t(3DC_s\varepsilon)/(r^2C_o\tau) \qquad \text{(Eq. 3.2)}$$

In equation 3.2, M_t/M_∞ is the fraction of drug released from the matrix at time t, D is the diffusivity of the drug in the dissolution medium, C_s is the solubility of the drug in the surrounding medium, C_o is the initial drug concentration in the matrix and r is the radius of the spherical system. The porosity and tortuosity of the matrix are represented by ε and τ, respectively.

As seen in Figure 3.4, theophylline release from the HME pellets was predominately diffusion-controlled in media below pH 7.4 as described by the Baker-Lonsdale model. The r^2 values for Apparatus 2 dissolution profiles in pH 1.0, 3.0 and 6.8 media were 0.9974, 0.9968 and 0.9899, respectively. Dissolution time points plotted represented less than 85% theophylline released. This model describes a diffusion-controlled drug release mechanism from an inert granular matrix when the matrix does not erode or dissolve over time. Drug release rate from HME pellets in pH 7.4 medium was not adequately described by the Baker-Lonsdale model (r^2 = 0.9469) since the matrix polymer is soluble in aqueous

media pH > 7.0. Thus, drug release behavior from the HME pellets in pH 7.4 medium was a result of both drug diffusion and matrix dissolution.

The USP paddle method (Apparatus 2) was employed to replicate transit through the human gastrointestinal tract. As illustrated in Figure 3.5, the wet-mass extruded beads exhibited rapid and complete theophylline release. In contrast, the HME beads displayed slower and more controlled drug release. At the 5 h time point, which included 1 h in pH 6.8, only 35% of the theophylline dose was released. The remaining theophylline was completely dissolved in the pH 7.4 medium within 3 h. Thus, the HME beads exhibited greater retardation of theophylline release than the wet-mass beads when using both the paddle and the reciprocating cylinder methods to quantify drug release.

The morphologies of formulation components were studied to further explain the drug release results from both the wet-granulated and the melt-extruded pellets. The dissolution rate of an API can depend on the morphology of the compound, with amorphous forms typically exhibiting faster dissolution rates than crystalline structures. Since thermal processing may alter the crystalline nature of matrix systems, the crystallinity of pellets was determined. Similar X-ray diffraction profiles were observed for pellets manufactured by both wet-mass extrusion and HME (Figure 3.6), which demonstrates that the crystallinity of the matrix system did not change significantly after thermal processing. Thus, changes in crystallinity did not account for differences in drug release rates from the two pellet types.

Furthermore, the high pressures employed during HME may have decreased the free-volume of the resulting extrudates, thus reducing the dissolution rate of theophylline from the melt-extruded pellets. Free-volume of

an amorphous material is defined as the volume that is not occupied by molecules of the material (Wicks 1986). Transport of materials in a closely packed system depends primarily on the degree of entanglement, or free-volume of the system, thus a matrix system with a low free-volume exhibits a slow drug release rate since the matrix network inhibits drug diffusion (Struik 1978).

Porous dosage forms usually exhibit faster drug release rates since these systems have more channels for water to enter and to dissolve the drug (Tongwen 1998). The effective porosity describes the space occupied by air inside a dosage form prior to the dissolution of the drug. Effective porosities of the wet-mass extruded and HME pellets, calculated using He pycnometry and Hg porosimetry determinations, were found to be significantly different ($n = 3$, student t-test, $p < 0.0005$ at $\alpha = 0.05$). The porosity of the wet-mass extruded beads was 6.09 ± 0.08%, whereas the porosity of the HME beads was 3.70 ± 0.08%. In addition to differences in porosity, researchers have also used the theory of tortuosity to explain slower release from thermally processed matrix systems since studies have indicated that thermal processing results in a more tortuous product (Foster 1990, Zang 2001). Tortuosity describes the directness of the path from the surface of the pellet to a void in the pellet. The pathway is more convoluted in a system with high tortuosity, making drug diffusion though the matrix pores more difficult.

Electron microscopy was used to qualitatively study the effect of the processing method on pellet porosity. The micrograph in Figure 3.7 represents the cross-sectional view of pellets at high magnification. Distinct drug and excipient particles are visible in the wet-mass extruded bead (3.7 A), while the HME bead (3.7 B) exhibited a less porous matrix. Drug and excipient particles

are more completely enclosed in the thermally processed composite due to interactions between solid particles and molten polymer chains (Foster 1990). Dispersed particles illustrated in the HME matrix are theophylline or MCC since these materials are not soluble in Eudragit® Preparation 4135 F under the studied processing conditions.

Researchers have employed post-processing thermal treatment of matrix systems to decrease drug release rate. Omelczuk and McGinity (1993) reported that thermal treatment of tablets containing PLGA above the *Tg* of the polymer significantly retarded drug release by promoting distribution of the polymer throughout the matrix and ensuring complete coalescence of the matrix polymer. Furthermore, Billa et al. (1998) found that thermal treatment of Eudragit® NE 40D containing matrix tablets reduced the rate of drug release due to formation of a matrix with higher tortuosity and lower porosity. Dissolution properties of HME and wet-mass extruded pellets were studied after storage for 24 h at 40°C or 60°C. Pellets were equilibrated for 24 h at 25°C/60 RH prior to dissolution testing. Dissolution profiles of heat-treated pellets were compared to the profiles of untreated pellets using a model independent approach to calculate difference (f_1) and similarity (f_2) factors (Guidance 1997). Generally, dissolution curves are considered equivalent when f_1 values are less than 15 and f_2 values are greater than 50. The comparison factors seen in Table 3.2 demonstrate that post-processing thermal treatment did not significantly influence theophylline release rate from either wet-mass extruded or HME pellets. Thus, curing had minimal effects on drug and polymer entanglement and polymer free-volume of the studied pellets.

3.4 CONCLUSIONS

Spherical pellets were successfully manufactured by a HME and spheronization process. HME and spheronization is a continuous process and does not require a lengthy drying step due to the absence of water or other solvents during manufacturing. Melt-extruded pellets exhibited a narrower particle size distribution in comparison with pellets prepared by conventional wet-mass extrusion. When the same dry powder formulation was employed, HME beads released theophylline more slowly than wet-mass extruded beads. Theoretical analysis of dissolution profiles indicated that theophylline release from HME pellets was a diffusion-controlled process as described by the Higuchi diffusion mode, and the drug release rates from HME pellets were not affected by the curing conditions studied. Furthermore, wet-granulated pellets did not exhibit diffusion-controlled drug release even after post-processing thermal treatment.

HME pellets can be employed in multitude of pharmaceutical applications since drug release rate is controlled by the properties of the matrix polymer. Conventional pellets must be coated to prevent rapid drug release, even when an insoluble matrix is used. Although HME pellets do not require a coating layer to prevent rapid drug release, melt-extruded pellets can be additionally modulated to further control drug release in the gastrointestinal tract.

3.5 REFERENCES

Aitken-Nichol, C.; Zhang, F.; McGinity, J.W Hot-melt extrusion of acrylic films. Pharmaceutical Research. 1996, 3, 804–808.

Andersson, M.; Holmquist, B.; Lindquist, J.; Nilsson, O.; Wahlund, K. Analysis of film coating thickness and surface area of pharmaceutical pellets using fluorescence microscopy and image analysis. Journal of Pharmaceutical and Biomedical Analysis. 2000, 22, 325-339.

Andreola, F.; Leonelli, C.; Romagnoli, M. Techniques used to determine porosity. American Ceramic Society Bulletin. 2000, July, 49-52.

Berner, B. and Dinh, S. Fundamental concepts in controlled release. In *Treatise on Controlled Drug Delivery*. Kydonieus, A., Ed.; Marcel Dekker: New York, 1992; 1-5.

Betageri, G., Kurumaddali, K. and Ravis, W., 1995, Preparation and in vitro evaluation of mefenamic acid sustained release beads. Drug Development and Industrial Pharmacy, 21, 265-275.

Bianchini, R.; Bruni, G.; Gazzaniga, A.; Vecchio, C. Influence of extrusion-spheronization on the physical properties of D-indobufen pellets containing pH adjusters. Drug Development and Industrial Pharmacy. 1992, 18, 1485-1503.

Billa, N.; Yuen, K.; Peh, K. Diclofenac release from Eudragit®-containing matrices and effects of thermal treatment. Drug Development and Industrial Pharmacy. 1998, 24, 45-50.

Costa, P.; Lobo, J.M.S. Modeling and comparison of dissolution profiles. European Journal of Pharmaceutical Sciences. 2001, 13 (2), 123-133.

Chopra, R.; Alderborn, G.; Podczeck, F.; Newton, J.M. The influence of pellet shape and surface properties on the drug release from uncoated and coated pellets. International Journal of Pharmaceutics. 2002, 239, 171-178.

Follonier, N.; Doelker, E.; Cole, E. Evaluation of hot-melt extrusion as a new technique for the production of polymer based pellets for sustained release capsules containing high loading of freely soluble drugs. Drug Development and Industrial Pharmacy. 1994, 20, 1323–1339.

Foster, T.; Parrott, E. Release of highly water-soluble medicinal compounds from inert, heterogeneous matrixes. II: melt. Journal of Pharmaceutical Sciences. 1990, 79, 938-942.

Gandhi, R.; Kaul; C.L.; Panchagnula, R. Extrusion and spheronization in the development of oral controlled-release dosage forms. Pharmaceutical Science and Technology Today. 1999, 2 (4), 160-170.

Ghali, E.S.; Klinger, G.H.; Schwartz, J.B. Thermal treatment of beads with wax for controlled release. Drug Development and Industrial Pharmacy. 1989, 15, 1311-1328.

Goskonda, S.R; Upadrashta, S.M. Avicel RC-591/chitosan beads by extrusion/spheronization technology. Drug Development and Industrial Pharmacy. 1993, 19, 815-927.

Guidance for industry: dissolution testing of immediate release solid oral dosage forms. 1997, http://www.fda.gov/cder/guidance/1713bp1.pdf (accessed June 2004).

Higuchi, T. Rate of release of medicaments from ointment bases containing drugs in solution. Journal of Pharmaceutical Sciences. 1961, 50, 874-875.

Higuchi, T. Mechanism of sustained-action medication. Journal of Pharmaceutical Sciences. 1963, 52, 1145-1149.

Levis, S.R.; Deasy, P.B. Pharmaceutical applications of size reduced grades of surfactant co-processed microcrystalline cellulose. International Journal of Pharmaceutics. 230, 25-33.

Lippold, B.C.; Pagés, R.M. Film formation, reproducibility of production and curing with respect to release stability of functional coatings from aqueous polymer dispersions. Die Pharmazie. 2001, 49, 243-252.

Liu, J.; Zhang, F.; McGinity, J.W. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. European Journal of Pharmaceutics and Biopharmaceutics. 2001, 52, 181-190.

Mehta, K.A.; Kislalioglu, M.S.; Phuapradit, W.; Malick, A.W.; Shah, N.H. Release performance of a poorly soluble drug from a novel, Eudragit-based multi-unit erosion matrix. International Journal of Pharmaceutics. 2001, 213, 7-12.

McGinity, J.W., Koleng, J.J., Repka, M.A. and Zhang, F., 2000, Hot-melt extrusion technology. In *Encyclopedia Pharmaceutical Technology,* 2nd

Ed.; Swarbrick, J.; Boilan, J.C., Eds.; Marcel Dekker: New York, 2000, Vol. 19, 203-226.

Omelczuk, M.O.; McGinity, J.W. The influence of thermal treatment on the physical-mechanical and dissolution properties of tablets containing poly(dl-lactic acid). Pharmaceutical Research. 1993, 10, 542-548.

Onay-Basaran, S.; Olsen, J. Formulation of long acting quinacrine hydrochloride pellets in different matrices. Part 1. Drug Development and Industrial Pharmacy. 1985, 11, 2143-2154.

Porter, S. Coating of pharmaceutical dosage forms. In *Remington: the Science and Practice of Pharmacy,* Limmer, D., Ed.; Lippincott: Baltimore, 2000, 894-902.

Repka, M.A.; Gerding, T.G.; Repka, S.L.; McGinity, J.W. Influence of plasticizers and drugs on the physical-mechanical properties of hydroxypropylcellulose films prepared by hot-melt extrusion. Drug Development and Industrial Pharmacy.1999, 25, 625–633.

Rubio, M.; Ghaly, E. In vitro release of acetaminophen from sodium alginate controlled release pellets. Drug Development and Industrial Pharmacy. 1994, 20, 1239-1251.

Struik, L.E. *Physical aging of amorphous polymers and other materials*. Elsiver: New York, 1978.

Tongwen, X.; Binglin, H. Mechanism of sustained drug release in diffusion-controlled polymer matrix-application of percolation theory. International Journal of Pharmaceutics. 1998, 170, 139-149.

Varner, J. Descriptive fractography, ceramics and glasses. Engineered Materials Handbook. 1991, 4, 634-644.

Vergote, G.J.; Vervaet, C.; Van Driessche, I.; Hoste, S.; De Smedt, S.; Demeester, J.; Jain, R.A.; Ruddy, S.; Remon, J.P. An oral controlled release matrix pellet formulation containing nanocrystalline ketoprofen, International Journal of Pharmaceutics. 2001, 219, 81-87.

Wheatley, T.A.; Steuernagel, C.R. Latex emulsions for controlled drug delivery. In *Aqueous Polymeric Coating for Pharmaceutical Dosage Forms*, McGinity, J.W., Ed.; Marcel Dekker: New York, 1997; Vol. 79, 19-41.

Wicks, Z.W. Free volume and coatings formulator. Journal of Coatings Technology, 1986, 58, 23-32.

Zhang, F.; McGinity, J.W. Properties of sustained release tablets prepared by hot-melt extrusion. Pharmaceutical Development and Technology. 1999, 4, 241–250.

Zhang, F.; McGinity, J.W. Properties of hot-melt-extruded theophylline tablets containing poly(vinyl acetate). Drug Development and Industrial Pharmacy. 2000, 26, 931-942.

Zhang, Y.E.; Tchao, R.; Schwartz, J.B. Effect of processing methods and heat treatment on the formation of wax matrix tablets for sustained drug release. Pharmaceutical Development and Technology. 2001, 6, 131-144.

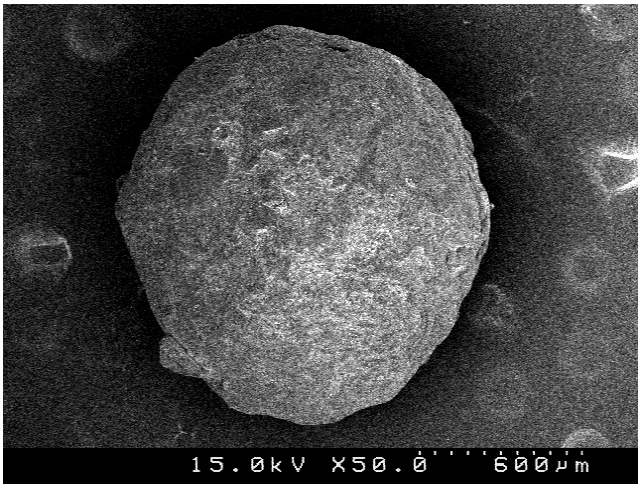
Table 3.1: The time point when at least 50% theophylline was released from wet-mass extruded and HME pellets in various dissolution media (USP 27 Apparatus 2, 900 mL, 37°C, 100 rpm, $n = 3$).

pH	Time (h)	
	Wet-Mass Extruded	**HME**
1.0	0.5	12
3.0	1	12
6.8	1	6
7.4	0.5	1

Table 3.2: Dissolution profile comparisons of wet-mass extruded and HME pellets following post-procession thermal treatment.

	Wet-Mass Extruded		**HME**	
Factor	**40°C**	**60°C**	**40°C**	**60°C**
f_1	2	3	2	2
f_2	76	69	93	91

A.



B.

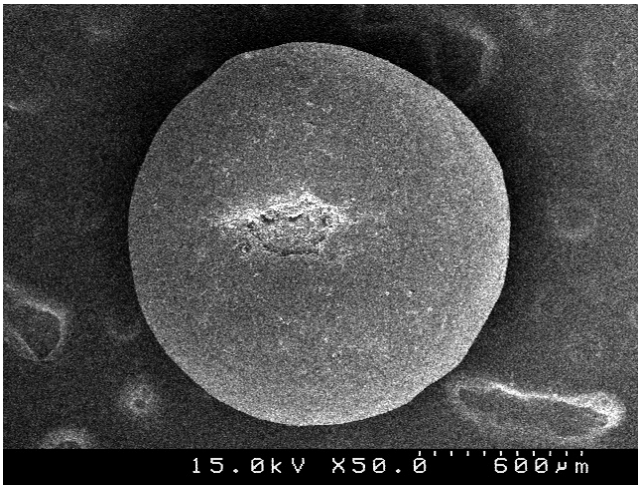


Figure 3.1: Low-magnification SEM micrographs of the surface of spherical pellets produced by two different techniques (approximately 1.2 mm diameter).

Key: A. Pellet produced by wet-mass extrusion and spheronization; B. Pellet produced by HME and spheronization.

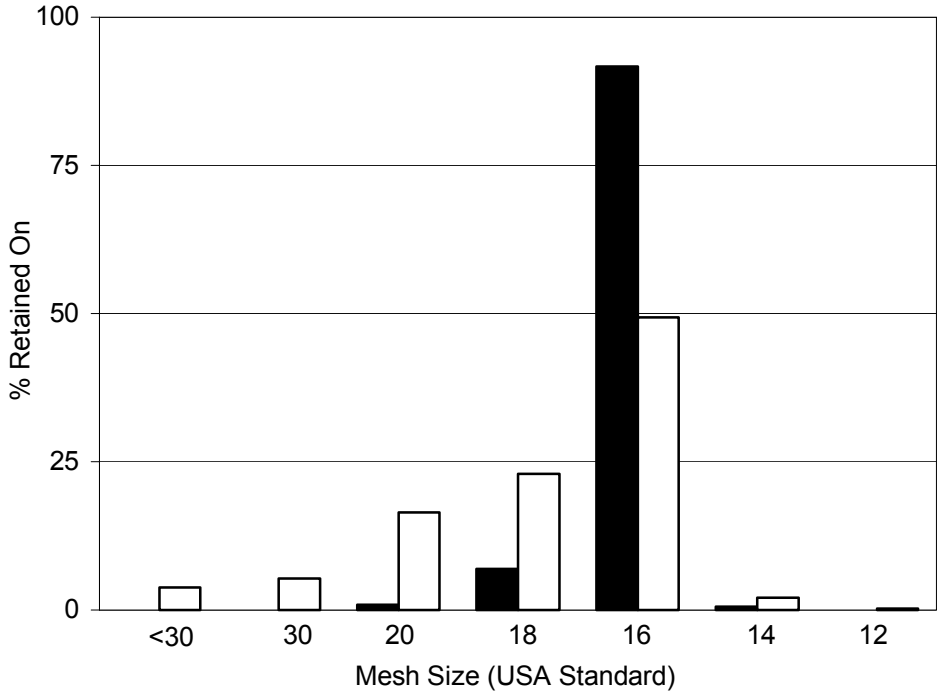


Figure 3.2: Particle size distribution of spherical pellets produced by two different techniques as determined by sieve analysis.

Key: □ Wet-mass extruded pellets; ■ HME pellets.

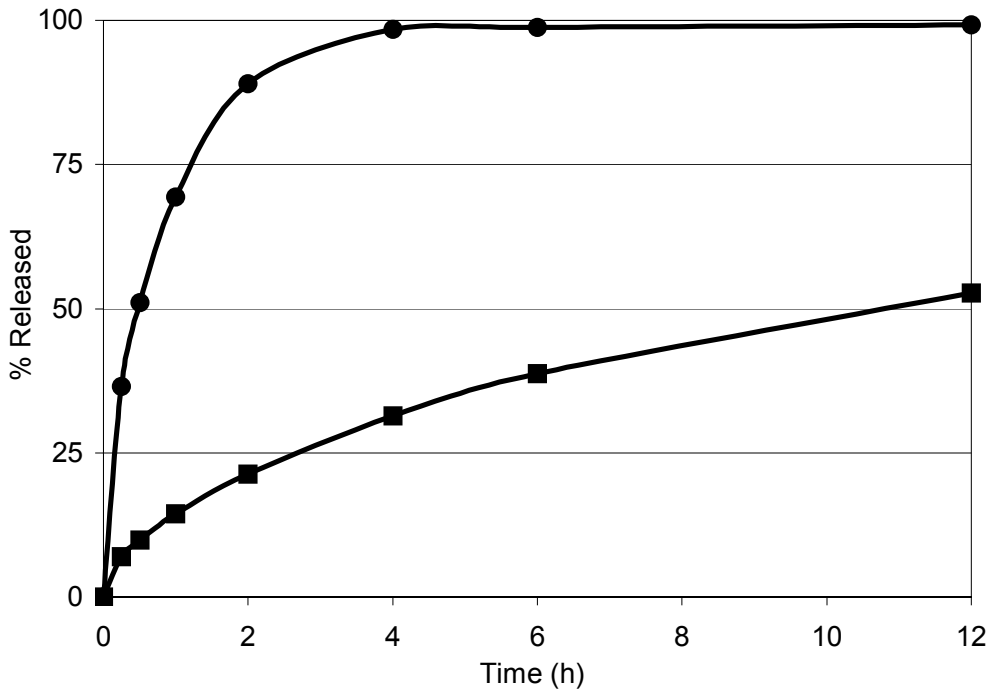


Figure 3.3: Dissolution in pH 1.0 medium of pellets prepared by two different techniques (USP 27 Apparatus 2, 900 mL, 37°C, 100 rpm, $n = 3$).

Key: ● Wet-mass extruded pellets; ■ HME pellets.

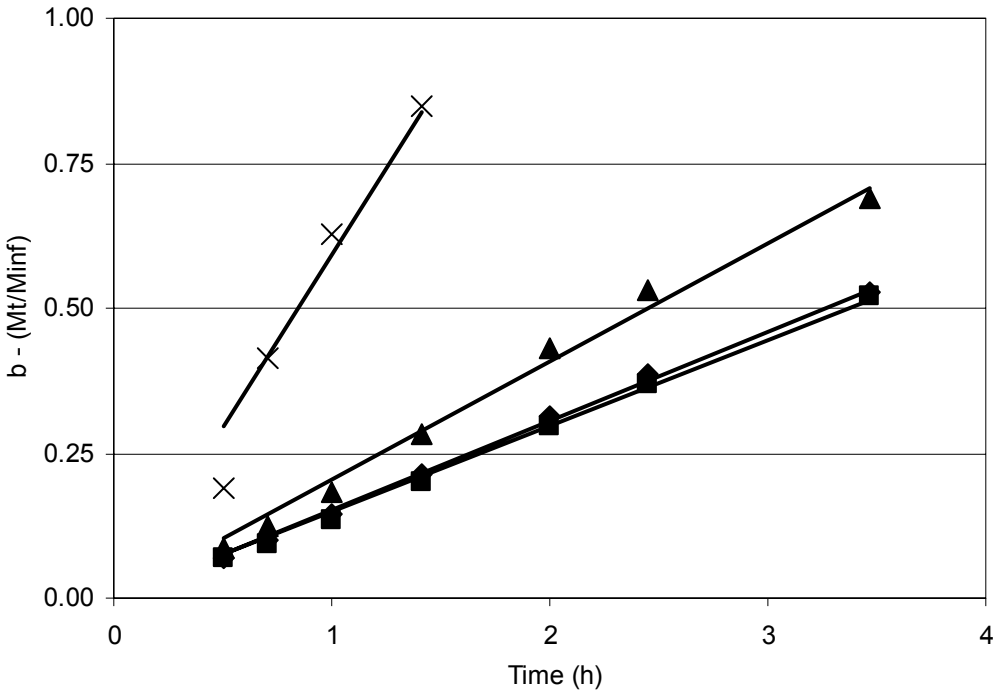


Figure 3.4: Baker-Lonsdale diffusion model fitting of theophylline release data from HME pellets, where $b = (3/2)[1 - (1 - (M_t/M_\infty))^{2/3}]$. (USP 27 Apparatus 2, 900 mL, 37°C, 100 rpm, $n = 3$).

Key: ◆ pH 1.0, $r^2 = 0.9974$; ■ pH 3.0, $r^2 = 0.9968$; ▲ pH 6.8, $r^2 = 0.9899$; ✕ pH 7.4, $r^2 = 0.9469$.

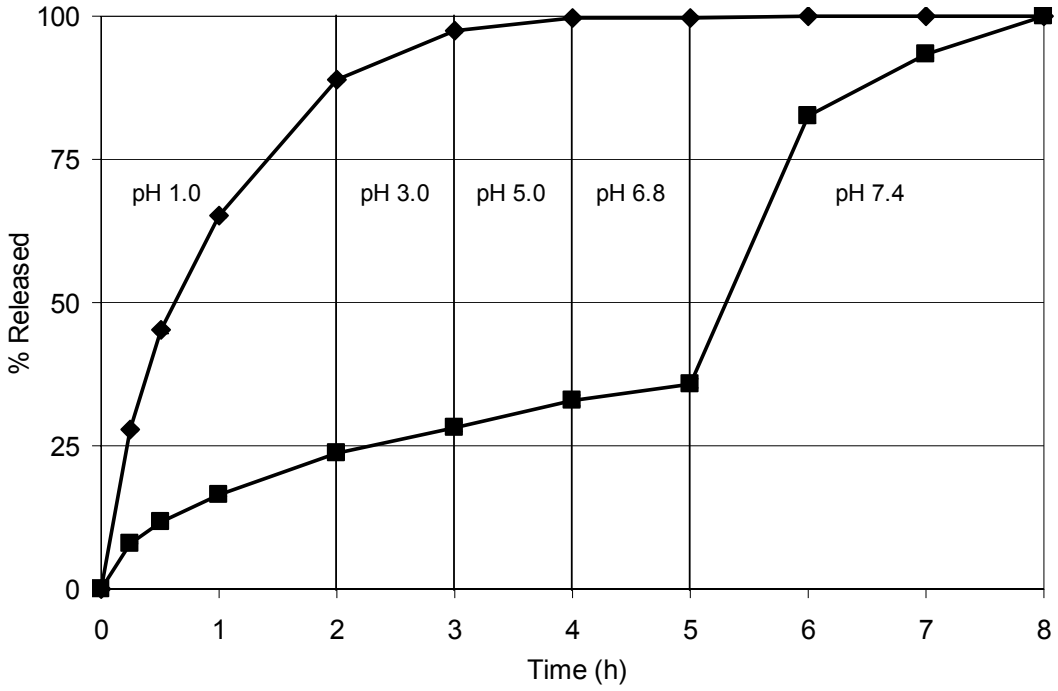


Figure 3.5: Influence of media pH on the release of theophylline from pellets produced by two different techniques (USP 27 Apparatus 3, 250 mL, 37°C, 20 dpm, $n = 3$).

Key: ● Wet-mass extruded pellets; ■ HME pellets.

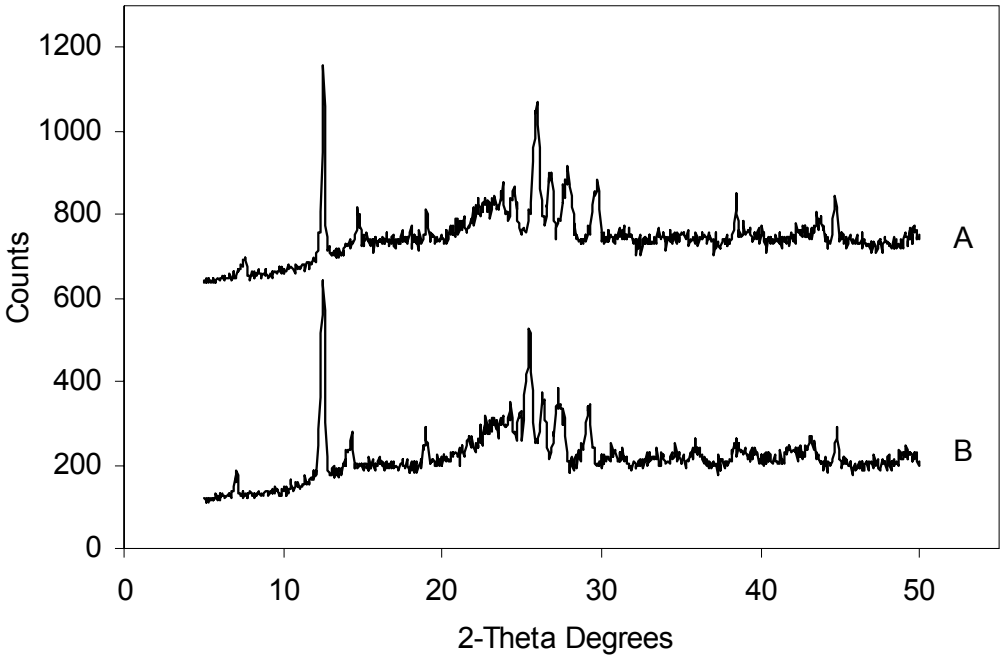
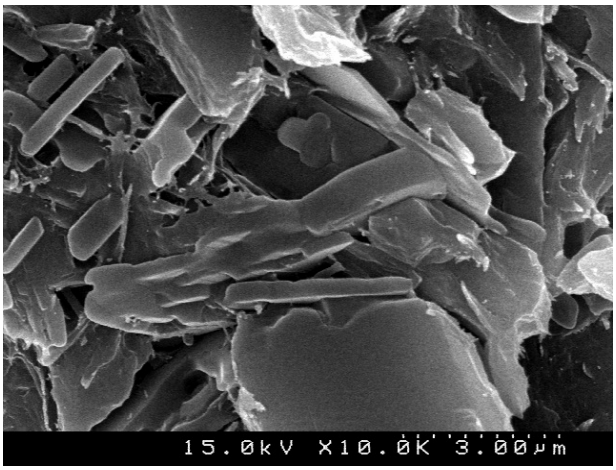


Figure 3.6: X-ray diffraction profiles of pellets manufactured by different processing methods.

Key: A. Wet-mass extrusion/spheronization; B. HME/spheronization.

A.



B.

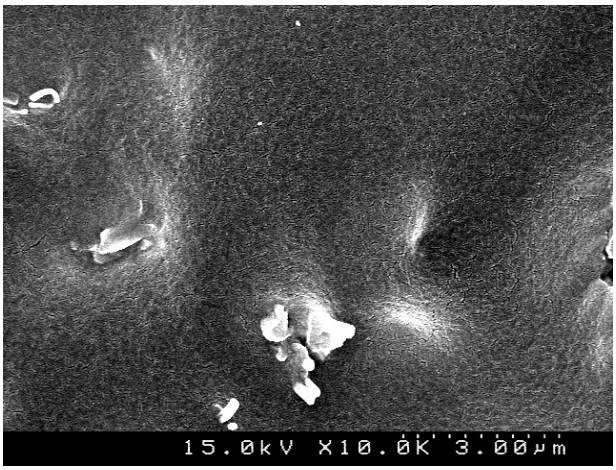


Figure 3.7: High-magnification SEM micrographs of the cross-section of pellets produced by two different techniques (approximately 1.2 mm diameter).

Key: A. Cross-section of pellet produced by wet-mass extrusion and spheronization; B. Cross-section of pellet produced by HME and spheronization.

Chapter 4: Compression of controlled-release pellets produced by a hot-melt extrusion and spheronization process

Manuscript in review, *Pharmaceutical Development and Technology*.

4.1 INTRODUCTION

Conventional drug therapy involves the periodic dosing of a therapeutic agent that has been formulated to ensure stability, activity and bioavailability of the active pharmaceutical ingredient (API). Nevertheless, many drugs present difficulties when administered by conventional methods due to toxicity and low therapeutic index problems. Controlled-release systems have been designed to maintain plasma drug levels in the therapeutic range and thus minimize the effects of such problems (Sood 2003). Furthermore, controlled-release systems reduce dosing frequency, thereby improving patient compliance and therapeutic efficacy (Sinha 2002). Although there are significant differences in the design and composition of marketed controlled-release dosage forms, these preparations can be broadly categorized as either single or multiple unit dosage forms.

The monolithic matrix-based tablet is an example of a single unit delivery system. The concept of the multiple unit dosage form was introduced in the early 1950s. These solid oral dosage forms consist of a multiplicity of small discrete particulates or pellets. Each unit exhibits desired drug release characteristics, and the pellets act together to provide the overall drug release profile. Thus, this system is less susceptible to dose dumping than the reservoir or matrix type, single unit dosage forms (Gandhi 1999). The individual elements are often granules or coated crystals.

Pellets offer advantages as constitutes of controlled-release systems since pellets are rapidly and evenly dispersed in the gastrointestinal tract upon oral administration, thus maximizing drug absorption and reducing inter- and intra-subject variability due to differences in gastric emptying rates (Sandberg 1988). Pellets can be filled into hard gelatin capsules or compressed into tablets, which rapidly disintegrate into multiple units. This dosage form is less susceptible to dose dumping than the reservoir or matrix type, single unit tablet since the drug release profile does not depend on the drug release properties of a single system (Erkoboni 2003). Additionally, multiparticulate tablets provide dosing flexibility since they can be scored and divided without compromising controlled-release properties of the individual units.

Nevertheless, the use of pellets as a dosage form is not without disadvantages. Wet-mass extrusion and spheronization, also termed cold-mass extrusion and spheronization, is the most frequently used method of producing spherical pellets. This process utilizes a granulating liquid such as water. The API can be included in the extruded pellet formulation or added onto the surface of non-pareil pellets. Drug-layering of non-pareil pellets employs the use of a binder solution, which is usually water based, to promote adhesion of the API onto the pellet surface. Thus, wet-mass extrusion and drug-layering require energy demanding and time consuming drying phases. Many drugs also exhibit stability problems due to the presence of water during processing and residual water during storage. Furthermore, pellets produced using these methods generally exhibit rapid drug release and require a film-coating to provide controlled-release properties, and coatings can be damaged during the tableting process.

A novel hot-melt extrusion (HME) and spheronization process was recently reported to produce spherical pellets without the use of water or other solvents (Young 2003). This method eliminates drug instability problems during processing due to water and ameliorates health, safety and environmental concerns due to solvents. Furthermore, pellets produced by melt-extrusion do not require an additional film-coating since drug release is diffusion controlled.

The aim of the current study was to investigate the physicomechanical and dissolution properties of tablets containing controlled-release pellets prepared by a HME and spheronization process. The effect of compression force on porosity and surface area was also studied. Furthermore, the influences of compression force, pellet to excipient ratio and filler excipient selection on the properties of pellet containing compacts was investigated using drug release, hardness, friability and disintegration time determinations.

4.2 MATERIALS AND METHODS

4.2.1 Materials

Eudragit® Preparation 4135 F (4135 F) is an experimental acrylic polymer that was donated by Röhm GmbH (Darmstadt, Germany). Anhydrous theophylline, USP was purchased from Spectrum Chemical (crystal shape and dimensions: needle, 80-100 μm x 100-400 μm; Gardena, CA). Polyethylene glycol 8000 powder (PEG, Carbowax® 8000) was supplied by Dow Chemical (Midland, MI). Povidone (PVP, Kollidon® 30) and sodium starch glycolate (Explotab®) were supplied by BASF (Mount Olive, NJ) and Penwest (Patterson, NY), respectively. Soy polysaccharides (Emcosoy®) was donated by Penwest (Patterson, NY), modified food starch (CerestarPharm® DC 93000) by Cerestar

(Hammond, IN), microcrystalline cellulose (MCC, Avicel® PH-102) by FMC (Newark, DE) and the 75:25 mixture of alpha-lactose monohydrate and microcrystalline cellulose (Microcelac® 100) by Meggle GmbH (Wasserburg, Germany). All materials were passed through a 30-mesh (600 μm) screen prior to processing.

4.2.2 Pellet and tablet production

The pellet formulation contained the thermal carrier 4135 F (48%), theophylline (30%), PEG 8000 (7%) and MCC (15%). The particle size of 4135 F granules was reduced to a fine powder (90% < 100μm) using a Micron Powder System Model CF cryogenic grinder (Summit, NJ). The formulation was mixed for 10 min in a twin-shell blender prior to melt-extrusion (Blend Master®, Patterson-Kelley, Stroudsberg, PA).

The powder blend was processed using a Randcastle Microtruder® RCP-0750 (Cedar Grove, NJ) single-screw extruder. The extruder temperatures employed were Zone 1 = 82°C, Zone 2 = 118°C, Zone 3 = 121°C and Die = 121°C. A cylindrical die 1.2 mm in diameter was used, and the extrudate was uniformly cut into cylindrical pellets using a Randcastle RCP-2.0 pelletizer. The pellets were marumerized for 15 min in a Caleva Model 120 spheronizer. A Milwaukee™ Model 1220 (International Tool Corporation; Davie, FL) heat gun was used to elevate the temperature of the spheronizer bowl to 60-70°C. The 14-16-mesh size (1.40-1.18 mm) pellets were used for compression studies. A detailed description of the HME and spheronization process was reported earlier (Young 2002).

Tablets weighing 500 mg were compressed using a Carver Model M laboratory press (Wabash, NJ) equipped with a 10 mm concave die. Pellets and

excipient mixtures were weighed separately and then physically mixed prior to compression at 5, 10, 15 and 20 kN. The tableting excipient mixtures consisted of 92% filler (MCC, alpha-lactose monohydrate:MCC, modified food starch or soy polysaccharides), 5% PVP and 3% sodium starch glycolate.

4.2.3 Effective porosity measurements

Pellet porosity measurements were calculated using the following equation for percent effective porosity (Varner 1991, Andreola 2000):

$$\%\varepsilon = \frac{(\rho_t - \rho_b)}{\rho_b} \text{ x } 100 \qquad \text{(Eq. 4.1)}$$

where ε = effective porosity, ρ_t = true density and ρ_b = bulk density. The true density of pellets cryogenically ground into fine powder was determined in triplicate using helium pycnometry (Micrometrics® AccuPyc 1330 pycnometer; Norcross, GA). Mercury porosimetry (Micrometrics® PoreSizer 9320; Norcross, GA) was employed to determine the bulk density of spherical pellets, in triplicate. Samples were stored at 25°C with desiccants under vacuum for 72 h prior to porosimetry and pycnometry determinations. Measurements were performed in triplicate.

4.2.4 Surface area determinations

The specific surface area was measured using a NOVA-2000 Version 6.11 instrument equipped with NOVA Enhanced Data Reduction Software Version 2.13 (Quantachrome Corporation; Boynton Beach, FL). A known amount of pellets (~300 mg) was transferred into a Quantachrome sample cell and degassed for at least 3 h prior to analysis.

4.2.5 Tablet characterization

Disintegration times were determined using an Erweka GmbH (Heusenstamm, Germany) disintegration tester with a dip rate of 20 dpm in 0.1 N HCl medium maintained at 37°C (n = 6), and tablet hardness was measured using a Heberlein (Switzerland) hardness tester (n = 6). A VanKel (Cary, NC) friabilator was used to determine tablet friability of a 6.5 g sample of tablets (n = 13). All experiments were performed according to USP 27 testing guidelines.

4.2.6 In vitro drug release studies

Dissolution testing of the theophylline containing pellets and tablets was conducted using the USP 27 Apparatus 3 dissolution testing guidelines (Reciprocating Cylinder Method, VanKel Bio-Dis II; Cary, NC) in 250 mL of medium at 37°C and 20 dpm. The media evaluated included pH 1.0 (0.1 N HCl), 3.0, 5.0, 6.8 and 7.4 (50 mM phosphate buffered solutions). The tablets transited through multiple media, including 2 h in pH 1.0, 1 h in pH 3.0, 5.0 and 6.8, and 3 h in pH 7.4. Dissolution studies on each formulation were performed in triplicate.

Dissolution samples were analyzed for theophylline content according to the USP 27 method using a Waters® HPLC system equipped with a photodiode array detector (Model 996) extracting at 281 nm. The column used was an Alltech Inertsil™ ODS-3 3 μm, 150 x 4.6 mm. The mobile phase contained a mixture of water:acetonitrile:glacial acetic acid in the volume ratios of 845:150:5 and 1.156 g/L of sodium acetate trihydrate. The flow rate was 1.5 mL/min, and the retention time of the theophylline was 3.6 min. Linearity was demonstrated from 1 to 100 mg/mL ($r^2 \geq 0.998$), and injection repeatability was 1% relative standard deviation for 6 injections.

4.3 RESULTS AND DISCUSSION

4.3.1 Influence of compression force

We recently reported that theophylline release from 4135 F containing HME pellets was predominately diffusion-controlled in media below pH 7.4 according to the Higuchi model, while the drug release rate was a result of both drug diffusion and matrix dissolution in pH 7.4 medium (Young 2003). The effective porosity and surface area are critical properties that influence the dissolution rate of drugs from controlled-release systems. Furthermore, previous workers have found that the surface area and porosity of wet-mass extruded pellets can be influenced by compression (Kühl 2002, Johansson 1995, Tunón 2001), and investigators have employed these measurements as indicators of compression-induced changes in drug release rate (Bechard 1992). Thus, tablets compressed using 50% pellets and MCC as the filler excipient were disintegrated in the dry state by shaking on metal sieves, and the pellets were studied using He porosity, Hg porosimetry and BET analysis. Light microscopy photographs of spheronized pellets before and after compaction at 20 kN are illustrated in Figure 4.1. The pellet effective porosity and surface area measurements were not influenced by compression force (Table 4.1, $n = 3$, one-way ANOVA, $\alpha = 0.05$). Thus, compression of molten materials during thermal extrusion prevented further densification of pellets during tableting.

Compression of pellets can either result in a disintegrating tablet that breaks into multiparticulates or a matrix tablet resulting from the fusion of film coatings. The effect of force on the properties of compacts containing 50% pellets and MCC is presented in Table 4.2. Tablet hardness increased with

compaction force, and forces of 15 and 20 kN produced tablets with hardness values exceeding the scale of the testing equipment. The disintegration times increased significantly with compression force, however, all tablets disintegrated without fusion of individual pellets. The 5 kN tablet disintegrated in 6 s, whereas the 20 kN tablet disintegrated after approximately 1 h. Nevertheless, tablet friability did not significantly change for compacts compressed at 10 to 20 kN, and only the 5 kN tablets demonstrated a friability value greater than 1%. The USP 27 considers a maximum weight loss of not more than 1% to be acceptable for most tablet formulations.

A significant challenge of tableting film-coated pellets is production of a multiparticulate dosage form without changing the drug release properties of the individual pellets (Bechard 1992, Flament 1994). The formation of a matrix tablet during compression due to fusion of polymer coated pellets usually results in a slower drug release rate. Even if the tablet disintegrates into multiparticulates, the film coatings could fracture during compression, accelerating the drug release rate (Sarisuta 1994). Thus, the influence of compaction force on the drug release rate of thermally processed pellets was investigated. The dissolution properties of tablets compressed with multiple forces and MCC as the filler excipient are shown in Figure 4.2. The rate of theophylline release in pH 3.0, 5.0, 6.8 and 7.4 media was identical for the compressed and uncompressed pellets, however, drug release in the 0.1 N HCl medium was influenced by compression force at 20 kN. The initial lag in theophylline release rate was due extension of the disintegration time to approximately 1 h which resulted from formation of strong compacts at high compression forces.

4.3.2 Influence of pellet to filler excipient ratio

The ratio of pellet to filler excipient has an important role in protecting pellets during compression (Bodmeier 1997). Filler excipients aid tablet compaction and are used to prevent direct contact between the pellets. Wagner and co-workers reported that based on theoretical calculations, a tablet formulation must contain at least 29% excipients to fill the void spaces between densely packed spheres. Coated pellets are more likely to be damaged and exhibit increased drug release rates as the content of filler excipients decreases (Wagner 2000). The influence of filler excipient content drug release properties was investigated in the current study by compressing tablets containing 50, 75 and 85% pellets. Compacts were produced using 5, 10, 15 and 20 kN of force and MCC as the filler excipient.

The dissolution and physical properties of compacts are illustrated in Table 4.3. Dissolution profiles were compared using a model independent approach to calculate difference and similarity factors, also known as f_1 and f_2 values. Generally, dissolution curves are considered equivalent when f_1 values are less than 15 and f_2 values are greater than 50 (Guidance 1997). Unlike many film-coated formulations, the dissolution rate of theophylline from compacts was not influenced by pellet content, even when high compression forces were employed. In all cases, the melt-extruded pellets did not fuse during compression as a result of pellet to pellet contact. However, tablets containing more than 50% pellets exhibited significant friability regardless of compression force. This finding was due to the poor compressibility of the dense HME pellets. Furthermore, previous researchers have noted decreased hardness and increased

friability of compacts containing high percentages of film-coated pellets produced by a non-thermal technique (Beckert 1996).

4.3.3 Influence of filler excipient properties

Excipients can protect multiparticulates during compression, and previous researchers have reported significantly different cushioning effects depending on the particle size and compaction properties of the excipient. Torrado and Augsburger (1994) studied the influence of excipients on the drug release rate of granules coated with Eudragit® RS. They found the order of least film damage to be: polyethylene glycol 3350 < microcrystalline cellulose < crospovidone < lactose < dicalcium phosphate. Previous investigators have produced pellets using soft materials to enhance compactability and cushioning effects (Nicklasson 1999, Lundqvist 1998). Vergote and coworkers (2002) found that wax beads functioned as a cushioning agent and provided protection to the film-coatings during compression. However, the dissolution rate of tablets formulated with waxy beads was too slow due to the poor disintegration properties of the tablets. Thus, protecting film-coated pellets during compression remains a significant problem.

In the current study, the influence of excipient selection on the drug release rate of theophylline from melt-extruded pellets was investigated by compressing tablets containing 50% pellets and four different filler excipients. The materials studied included MCC (Avicel® PH-102), a 75:25 mixture of alpha-lactose monohydrate:MCC (Microcelac® 100), modified food starch (CerestarPharm® DC 93000) and soy polysaccharides (Emcosoy®). Each excipient and pellet mixture was compressed at 5, 10, 15 and 20 kN of force. None of the excipient and compression force combinations significantly

influenced the drug release rate in the pH 3.0, 5.0, 6.8 or 7.4 media. High compression forces of MCC and alpha-lactose:MCC containing compacts exhibited delayed drug release in the 0.1 N HCl medium due to extended disintegration times caused by formation of strong compacts at high compression forces. The drug release profiles were identical to those of uncompressed pellets after transition to the pH 3.0 medium. The influence of the filler excipient on theophylline release from tableted pellets using a compression force of 15 kN is illustrated in Figure 4.3. Only the formulation employing the alpha-lactose monohydrate:MCC mixture as the filler excipient exhibited slow tablet disintegration. Thus, only the dissolution profile in acid of compressed HME pellets was significantly influenced by filler excipient selection.

4.4 CONCLUSIONS

Melt-extruded pellets containing Eudragit® Preparation 4135 F were found to be an ideal substrate for compression into tablets since compression force, pellet to excipient ratio and filler excipient selection did not influence the theophylline release rate from rapidly disintegrating compacts. Furthermore, tableting did not influence the effective porosity or surface area of pellets since compression of molten materials during thermal extrusion produces dense extrudates. These findings represent a significant advantage of HME matrix pellets over film-coated pellets which are frequently damaged during compression.

4.5 REFERENCES

Andreola, F.; Leonelli, C.; Romagnoli, M. Techniques used to determine porosity. American Ceramic Society Bulletin. 2000, July, 49-52.

Bechard, S.; Leroux, J. Coated palletized dosage form: effect of compaction on drug release. Drug Development and Industrial Pharmacy. 1992, 18 (Mar), 1927-1944.

Beckert, T.; Lehmann, K.; Schmidt, P. Compression of enteric-coated pellets to disintegrating tablets. International Journal of Pharmaceutics. 1996, 43 (1), 13-23.

Bodmeier, R. Tableting of coated pellets. European Journal of Pharmaceutics and Biopharmaceutics. 1997, 43 (1), 1-8.

Erkoboni, D.F. Extrusion/Spheronization. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 277-322.

Flament, M.-P.; Leterme, P.; Gayot, A.; Gendrot, E.; Bruna, E. Development and industrial scale-up of tablets containing modified-release pellets. Pharmaceutical Technology Europe. 1994, 6, 19-25.

Gandhi, R.; Kaul; C.L.; Panchagnula, R. Extrusion and spheronization in the development of oral controlled-release dosage forms. Pharmaceutical Science and Technology Today. 1999, 2 (4), 160-170.

Guidance for industry: dissolution testing of immediate release solid oral dosage forms. 1997, http://www.fda.gov/cder/guidance/1713bp1.pdf (accessed June 2004).

Johansson, B.; Wikberg, M.; Ek, R.; Alderborn, G. Compression behaviour and cmpactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical properties. International Journal of Pharmaceutics. 1995, 117 (1) 57-73.

Kühl, P.; Mielck, J. Tabletting of pellet–matrix systems: ability of parameters from dynamic and kinetic models to elucidate the densification of matrix formers and of pellets. International Journal of Pharmaceutics. 2002, 248 (1-2), 101-114.

Lundqvist, Å.E.K.; Podczeck, F.; Newton, J.M. Compaction of, and drug release from, coated drug pellets mixed with other pellets. European Journal of Pharmaceutics and Biopharmaceutics. 1998, 46, 369-379.

Nicklasson, F.; Alderborn, G. Modulation of the tabletting behaviour of microcrystalline cellulose pellets by the incorporation of polyethylene glycol. European Journal of Pharmaceutical Sciences. 1999, 9 (1), 57-65.

Sandberg, A.; Blomqvist, I.; Jonsson, U.; Lundborg, P. Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol: a comparison with conventional tablets. European Journal of Clinical Pharmacology. 1988, 33 (Suppl.), S9–S14.

Sarisuta, N.; Punpreuk, K. In vitro properties of film-coated diltiazem hydrochloride pellets compressed into tablets. Journal of Controlled Release. 1994, 31 (3), 215-222.

Sinha, V.; Trehan, A., 2003, Biodegradable microspheres for protein delivery. Journal of Controlled Release. 2002, 90 (3), 261-280.

Sood, A.; Panchagnula, R. Design of controlled release delivery systems using a modified pharmacokinetic approach: a case study for drugs having a short elimination half-life and a narrow therapeutic index. International Journal of Pharmaceutics. 2003, 261 (1-2), 27-41.

Torrado, J.; Augsburger, L. Effect of different excipients on the tableting of coated particles. International Journal of Pharmaceutics. 1994, 106 (2), 149-155.

Tunón, Å; Alderborn, G. Granule deformation and densification during compression of binary mixtures of granules. International Journal of Pharmaceutics. 2001, 222 (1), 65-76.

Tunón, Å.; Gråsjö, J.; Alderborn, G. Effect of intragranular porosity on compression behaviour of and drug release from reservoir pellets. European Journal of Pharmaceutical Sciences. 2003, 19 (5), 333-344.

Varner, J. Descriptive fractography, ceramics and glasses. Engineered Materials Handbook. 1991, 4, 634-644.

Vergote, G.; Kiekens, F.; Vervaet, C.; Remon, J. Wax beads as cushioning agents during the compression of coated diltiazem pellets. European Journal of Pharmaceutical Sciences. 2002, 17 (3), 145-151.

Wagner, K.; Krumme; M., Beckert, T.; Schmidt, P. Development of disintegrating multiple-unit tablets on a high-speed rotary tablet press. European Journal of Pharmaceutics and Biopharmaceutics. 2000, 50, 285-292.

Young, C.R.; Koleng, J.J.; McGinity, J.W. Properties of drug-containing spherical pellets produced by a hot-melt extrusion and spheronization process. Journal of Microencapsulation. 2003, 20 (5), 613-625.

Young, C.R.; Koleng, J.J.; McGinity, J.W. Production of spherical pellets by a hot-melt extrusion and spheronization process. International Journal of Pharmaceutics. 2002, 242 (1-2), 87-92.

Table 4.1: Influence of compression force on properties of pellets from compacts containing 50% pellets and MCC as the filler excipient (one-way ANOVA, $n = 3$, $\alpha = 0.05$).

PROPERTY \ FORCE	Uncompressed HME Pellets	5 kN	10 kN	15 kN	20 kN
Surface Area (m^2/g) *	0.256 ± 0.02	0.264 ± 0.02	0.262 ± 0.03	0.266 ± 0.02	0.270 ± 0.03
% Effective Porosity *	3.70 ± 0.08	3.72 ± 0.09	3.67 ± 0.05	3.68 ± 0.10	3.65 ± 0.11

* No statistical difference

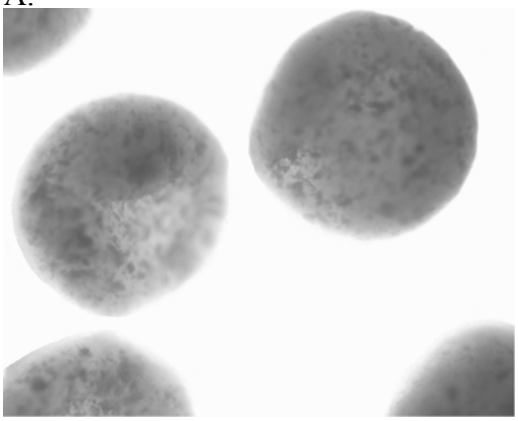
Table 4.2: Influence of compression force on tablet properties using a formulation of 50% pellets and MCC as the filler excipient (Hardness and Disintegration, $n = 6$; Friability, $n = 13$).

PROPERTY \ FORCE	5 kN	10 kN	15 kN	20 kN
Hardness (Kg)	5.3 ± 0.9	14.5 ± 1.5	>16	>16
Disintegration Time (Min)	0.09 ± 0.02	1.37 ± 0.05	18.6 ± 3.2	53.4 ± 3.5
Friability (% Weight Loss)	1.22	0.08	0.07	0.07

Table 4.3: Influence of compression force and pellet content on tablet properties using MCC as the filler excipient (Dissolution, $n = 3$; Hardness and Disintegration, $n = 6$; Friability, $n = 13$).

PELLET CONTENT	PROPERTY \ FORCE	5 kN	10 kN	15 kN	20 kN
50%	f_1	0.9	1.1	1.6	1.5
	f_2	93.8	94.5	86.0	82.7
	HARDNESS (Kg)	5.30	14.5	>16	>16
	DISINTEGRATION TIME (Min)	0.09	1.37	18.60	53.40
	FRIABILITY (% Weight Loss)	1.22	0.08	0.07	0.07
75%	f_1	2.0	1.7	1.4	1.5
	f_2	82.6	82.4	89.4	87.2
	HARDNESS (Kg)	3.75	11	>16	>16
	DISINTEGRATION TIME (Min)	0.32	0.82	1.47	1.73
	FRIABILITY (% Weight Loss)	28.48	20.73	9.50	4.79
85%	f_1	1.1	0.8	1.2	2.2
	f_2	93.9	96.7	86.1	79.6
	HARDNESS (Kg)	3.00	7.5	>16	>16
	DISINTEGRATION TIME (Min)	0.96	1.64	2.69	2.29
	FRIABILITY (% Weight Loss)	47.67	31.80	26.08	20.91

A.



B.

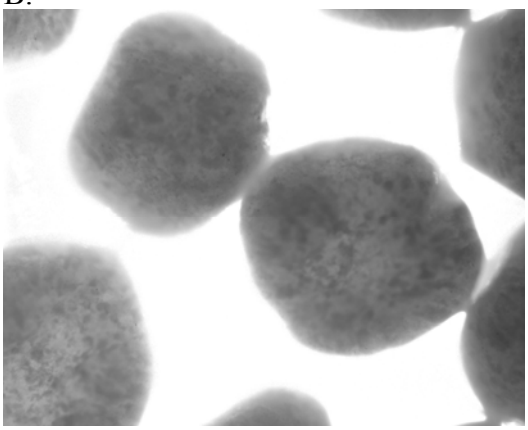


Figure 4.1: Light microscopy photographs of HME and spheronized pellets (approximately 1.2 mm diameter pellets at 10x magnification) before and after compression with 20 kN of force.

Key: A. Uncompressed HME pellets; B. Compressed HME pellets.

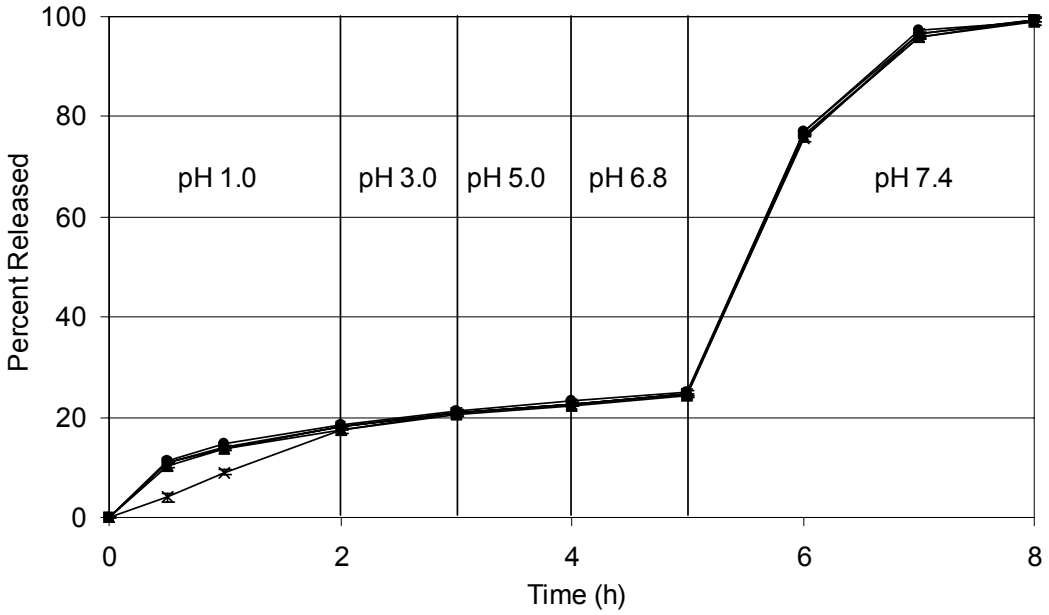


Figure 4.2: The influence of compression force on the theophylline release profile of compressed HME pellets using 50% pellet content and MCC as the filler excipient (USP 27 Apparatus 3, 250 mL, 37°C, 20 dpm, $n = 3$).

Key: ● Initial pellets; ◆ 5 kN; ■ 10 kN; ▲ 15 kN; ✕ 20 kN.

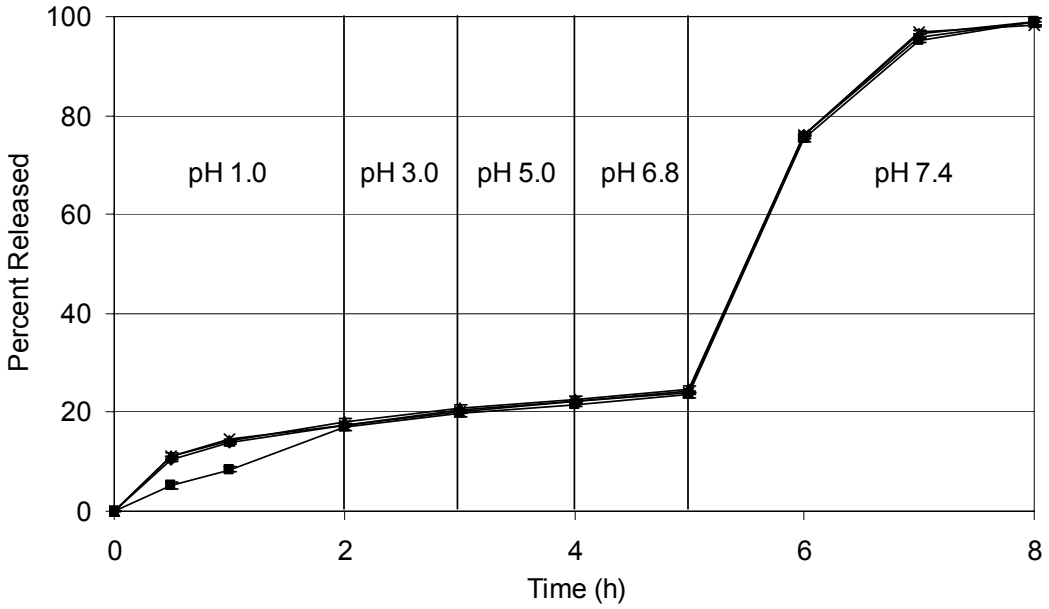


Figure 4.3: The influence of filler excipient selection on the theophylline release profile of compacts using 50% pellet content and 15 kN as the compression force (USP 27 Apparatus 3, 250 mL, 37°C, 20 dpm, *n* = 3).

Key: ◆ MCC; ■ Alpha-lactose monohydrate:MCC, 75:25; ▲ Modified food starch; ✕ Soy polysaccharides.

Chapter 5: Physicochemical properties and film-coating of a melt-extruded and spheronized solid dispersion for pH-dependent drug delivery

5.1 INTRODUCTION

Controlled drug release systems offer several advantages over conventional drug therapies that involve periodic dosing of therapeutic agents. Drug delivery systems have been designed to maintain plasma drug levels in the therapeutic range and thus minimize toxicity and narrow therapeutic index problems (Sood 2003). Controlled release dosage forms can also improve patient compliance and therapeutic efficacy by reducing dosing frequency (Sinha 2002). Beads have been widely studied as controlled release dosage forms since they can be film coated with functional polymers to sustain, delay or target drug release. Furthermore, pellets can be delivered in hard gelatin capsules or tablets for controlled drug delivery applications. A novel hot-melt extrusion (HME) and spheronization process was recently reported to produce controlled release beads without the need for film-coating (Young 2002, Young 2003).

Poly(ethylene oxide) is a semi-crystalline, high molecular weight, water-soluble polymer which is used in sustained-release applications, oral suspensions and suppositories due to its swelling and mucoadhesive properties. The long linear chain structure of the polymer forms a strong interpenetrating network with mucus. Previous researchers have investigated the properties of bioadhesive films and matrix tablets containing poly(ethylene oxide) produced by melt-extrusion (Zhang 1999, Repka 2000, Crowley 2002), but thermally processed bead systems have not been studied. Furthermore, film-coating applications have

not been investigated to control drug release from melt-extruded matrix systems containing a low melting point thermoplastic carrier.

The purpose of the current study was to investigate the physicochemical properties of poly(ethylene oxide) beads produced by a novel melt-extrusion process and film-coated with a pH-dependent polymer. The calculated solubility parameters and thermal properties of materials were used to determine the suitability of systems for melt-extrusion. Following thermal processing, the influence of accelerated storage conditions on the drug release and physiochemical properties of pellets was studied. Furthermore, film-coating of melt-extruded beads with Eudragit® L 30 D-55 was studied to design a pellet system with pH-dependent drug release properties.

5.2 MATERIALS AND METHODS

5.2.1 Materials

Guaifenesin was purchased from Spectrum Laboratory Products (Gardena, CA). Poly(ethylene oxide) (PEO; Polyox™ WSR-301, Mw. 4,000,000) and ethylcellulose (Ethocel® 100FP Premium) were kindly donated by the Dow Chemical Company (Midland, MI). Glyceryl monostearate (GMS; Imwitor® 491) was contributed by Sasol (Witten, Germany). Eudragit® L 30 D-55 and triethyl citrate (TEC) were donated by Röhm (Darmstadt, Germany) and Morflex (Greensboro, NC), respectively. HPLC solvents were purchased from EM Science (Gibbstown, NJ).

5.2.2 Calculation of solubility parameters

The Hansen solubility parameters of guaifenesin and PEO were calculated from the chemical structures using the group contribution method described by Van Krevelen and Hoftyzer (Van Krevelen 1990).

$$\delta_t^2 = \delta_d^2 + \delta_p^2 + \delta_h^2 \quad \text{(Eq. 5.1)}$$

$$\delta_d = (\Sigma F_{di}) / V \quad \text{(Eq. 5.2)}$$

$$\delta_p = (\Sigma F_{pi}^2)^{1/2} / V \quad \text{(Eq. 5.3)}$$

$$\delta_h = [(\Sigma E_{hi}) / V]^{1/2} \quad \text{(Eq. 5.4)}$$

where, δ_t = Total solubility parameter

δ_d = Contribution of dispersion forces

δ_p = Contribution of polar forces

δ_h = Contribution of hydrogen bonding

F_{di} = Molar attraction constant due to dispersion component

F_{pi} = Molar attraction constant due to polar component

E_{hi} = Hydrogen bonding energy

V = Molar volume

For the polymeric excipient, determination of the solubility parameters was based on the average molecular weight of 4,000,000. The units of the reported solubility parameters are $MPa^{1/2}$, where 1 $MPa^{1/2}$ is equivalent to 0.4888 $(cal \cdot cm^{-3})^{1/2}$.

5.2.3 Thermal analysis

Thermal gravimetric analysis (TGA) of pellet formulation components and blends was performed with a Perkin Elmer TGA 7 using a heating rate of

10°C/min from 50°C to 600°C. The melting points of individual components and physical blends were determined by modulated differential scanning calorimetry (MDSC, TA Instruments Model 2920; New Castle, DE) using a heating rate of 5°C/min over a temperature range of –20°C to 165°C. The reported melting point was determined from the second heating cycle. Volatiles were removed from samples by storing powders under vacuum with desiccants at 25°C for 72 h prior to thermal studies. MDSC analysis of samples was performed in triplicate.

5.2.4 Spherical pellet production

Pellet formulations containing guaifenesin, PEO, ethylcellulose and GMS are detailed in Table 5.1. The blends were prepared by geometric dilution, introduced into a V-blender (Blend Master®, Patterson-Kelley, East Stroudsburg, PA) and mixed for 15 min. The powders (500 g) were fed into a single-screw Randcastle Microtruder® (Model RCP-0750, Cedar Grove, NJ) equipped with a Nitralloy 135M screw (3:1 compression ratio with flight configuration containing feed, compression and mixing sections) and a 1.5 mm cylindrical die. Screw speed was maintained at 15 rpm. The three heating zones and die temperatures were equilibrated to 60, 75, 85 and 95°C, respectively. Residence time of the materials in the extruder was approximately 5 min.

The extrudates were uniformly cut into cylindrical pellets using a Randcastle RCP-2.0 pelletizer and then merumerized for 15 min in a Caleva Model 120 spheronizer. A Milwaukee™ Model 1220 (International Tool Corporation; Davie, FL) heat gun was used to elevate the temperature of the spheronizer bowl to 60-70°C. Spherical pellets were stored in sealed HDPE

containers with silica desiccants at 40°C/75% RH. Beads produced by this novel HME and spheronization process are illustrated in Figure 5.1.

5.2.5 Film-coating

A 30% (w/w) dispersion of Eudragit® L 30 D-55 was diluted to 15% (w/w) solids content based on dry polymer weight. TEC, 15% (w/w) based on the dry polymer content, was added to the polymeric dispersion and stirred for 30 min. Talc, 50% (w/w) based on dry polymer weight, was dispersed in water using a Polytron® mixer (Brinkmann Instruments, Westbury, NY) and then combined with the plasticized Eudragit® L 30D-55 prior to coating.

The coating dispersion was applied to a 250 g charge of HME beads using a Strea 1 fluidized bed coater (Strea I, Niro Inc., Columbia, MD) with bottom spray and a Wurster column insert. The coating conditions were as follows: inlet temperature 40°C, outlet temperature 32-34°C, spray rate 4 g/min, nozzle diameter 1 mm and atomization pressure 1.75 bar. The coated pellets were cured at 40°C for 24 h and then stored at 40°C/75% RH in sealed HDPE containers with silica desiccants.

5.2.6 In vitro drug release studies

Dissolution testing of uncoated beads was conducted using USP 27 Apparatus 2 (paddle method) guidelines (Van Kel VK7000; Cary, NC) in 900 mL of 0.1 N HCl maintained at 37°C and agitated at 100 rpm. The enteric properties of coated products were studied according to Method A, which included 2 h in an acidic stage (pH 1.0, 0.1 N HCl, 750 mL) followed by testing in a buffered stage (pH 6.8) upon the addition of 250 mL of 0.2 M sodium

phosphate tribasic. Pellets stored at accelerated conditions were equilibrated at 25°C for 24 h before dissolution investigations.

Dissolution samples were analyzed for guaifenesin content using a Waters® HPLC system equipped with a photodiode array detector (Model 996) extracting at 276 nm. The data were collected and integrated using Empower® Version 5.0 software. The column used for guaifenesin analysis was an Alltech Alltima™ C_{18} 10 μm, 250 x 4.1 mm. The mobile phase contained a mixture of water:methanol:glacial acetic acid in volume ratios of 600:400:15. Solvents were vacuum filtered though a 0.45 μm nylon membrane and degassed using a Waters In-Line Degasser AF. The flow rate was 1.5 mL/min, and the retention time of guaifenesin was 3.0 min. Linearity was demonstrated from 2 to 200 mg/μL ($r^2 \geq$ 0.998), and injection repeatability was 0.35% relative standard deviation for 10 injections.

5.2.7 Weight loss on drying

The amount of volatiles in pellet samples was determined gravimetrically using the USP 27 method for weight loss on drying of guaifenesin. Samples weighing approximately 2 g were dried at 60°C under a vacuum with desiccants for 5 days. The dried pellets were equilibrated at 25°C under a vacuum with desiccants for 24 h before reweighing.

5.2.8 Tortuosity and effective porosity measurements

The tortuosity and bulk density of pellets were determined using an AutoPore IV 9500 mercury intrusion porosimeter (Micromeritics, Norcross, GA). Approximately 3 g of pellets were placed in a 5 cc bulb penetrometer, and pressure was applied from 1 to 15,000 psia. The technique for measuring

tortuosity using mercury porosimetry was previously described by Crowley et al. (Crowley 2004).

Pellet porosity measurements were calculated using equation 1 for percent effective porosity (Varner 1991, Andreola 2000):

$$\% \ \varepsilon = [(\rho_t - \rho_b) / \rho_b] \text{ x } 100 \qquad \text{(Eq. 5.5)}$$

where ε = effective porosity, ρ_t = true density and ρ_b = bulk density. The true density of pellets cryogenically ground into fine powder was determined using helium pycnometry (Micrometrics® AccuPyc 1330 pycnometer; Norcross, GA). Samples were stored at 25°C with desiccants under vacuum for 72 h prior to porosimetry and pycnometry determinations. Measurements were performed in triplicate.

5.2.9 Scanning electron microscopy

The surface morphology of gold:palladium (60:40, Ted Bench Top Sputter Coater; Redding, CA) coated beads was examined using a Hitachi S-4500 field emission scanning electron microscope (Rolling Meadows, IL).

5.2.10 Powder X-ray diffraction

The crystalline properties of formulation components and melt-extruded pellets were examined using a Philips PW 170 X-ray generator equipped with a PW 1710 X-ray diffractometer. The operating current and voltage were 40 mA and 40 kV, respectively. Samples were examined using a 2-theta scanning range from 5° to 55°, a step size of 0.05° and a dwell time of 1 s.

5.3 RESULTS AND DISCUSSION

5.3.1 Calculation of solubility parameters

Previous researchers have demonstrated the potential of melt-extrusion to form solid dispersions (Gruenhagen 1996, Breitenbach 2002, Forster 2001). The advantages of using melt-extrusion over solvent-based systems to form molecular solid dispersions include absence of residual solvents, decreased environmental implications, decreased costs and the possibility of continuous processing (Gruenhagen 1996). Molecular solid dispersions are defined as a molecular embedding in a carrier that is a glass or crystalline matrix (Breitenbach 2003).

Ideally, drugs processed to form molecular solid dispersions should exhibit unlimited solubility in the carrier, but this is rarely the case and supersaturated systems are often produced. These dispersions bear the risk of reverting back to the more stable crystalline form, thus creating morphologically unstable products. Thus, the solid-state solubility of the drug in the carrier material is important to consider when developing a solid dispersion. Calculation of solubility parameters has been employed by several researchers to predict the miscibility of drugs and excipinets (Suzuki 1997, Greenhalgh 1999, Hancock 1997).

Currently, the most widely accepted group contribution method for calculation of solubility parameters is the three component system developed by Charles Hansen, which divides the total Hildebrand value into: a dispersion force component, a hydrogen bonding component and a polar component (van Krevelen 1990). Compounds with similar total solubility parameters (δ_t) are likely to be miscible since the energy of mixing from intramolecular interactions

is balanced with the energy of mixing from intermolecular interactions. Greenhalgh and coworkers (1999) used the difference between the total solubility parameters ($\Delta\delta_t$) of materials to estimate miscibility, concluding that that compounds with $\Delta\delta_t < 7$ MPa$^{1/2}$ were likely to be miscible and that compounds with $\Delta\delta_t > 10$ MPa$^{1/2}$ were likely to be immiscible. The solubility parameters calculated using the group contribution method as described by Van Krevelen and Hoftyzer (Van Krevelen 1990) are seen in Table 5.2. Guaifenesin and PEO are likely to exhibit partial or complete miscibility since the $\Delta\delta_t$ is 2.99 MPa$^{1/2}$.

5.3.2 Thermal studies

The thermal properties of materials and powder blends were studied to determine drug/polymer miscibility and processing parameters. Extrusion temperature is critical due to the potential thermal instability of formulation components during processing. The MDSC thermograms of pure guaifenesin, PEO and melt-extruded blends of the materials are shown in Figure 5.2. Although guaifenesin alone was characterized by a strong melting transition at 82.6°C, the transition was not detected in the extrudates containing PEO. The absence of a guaifenesin melting point after co-extrusion with PEO suggested miscibility of the blend and supported the prediction of the calculated solubility parameters.

The melting point of a material is dependent upon the crystal lattice of the solid. Impurities in a material break up the regular, repeating molecular pattern of the crystal lattice and thus result in broadening of the melting range and depression of the melting point (Vogel 1996). Introduction of guaifenesin broadened the melting range and decreased the melting point of PEO. Furthermore, the thermograms exhibited depression of the melting transition with

increasing guaifenesin concentration. Several researchers have noted that reduction of the melting point or glass transition temperature of the carrier material facilitates thermal processing by decreasing barrel pressure, drive amps, torque and the propensity for degradation of the API and other matrix components (Repka 2000, Crowley 2002, Zhu 2002).

The thermal stability of materials was studied using TGA and HPLC. As illustrated in Figure 5.3, TGA was employed to determine the temperature at which weight loss due to degradation was observed for individual formulation components and physical blends. Guaifenesin exhibited weight loss at approximately 200°C, which was well below the processing temperatures of 60 to 95°C. Furthermore, the chemical stability of guaifenesin after melt-extrusion was verified using a stability indicating reversed-phase HPLC method. Thus, the drug and formulation components were thermally stable at the processing conditions.

5.3.3 Drug release properties and physical stability of pellets

PEO hydrates to form a gel layer upon contact with an aqueous medium due to strong hydrogen bonding between the polyether chains of the polymer and water molecules. The hydrogel erodes as the polymer dissolves. Thus, drug release form PEO matrices is controlled by a combination of polymer swelling, erosion and drug diffusion through the hydrated gel (Di Colo 2001). Melt-processed pellets were stored in sealed HDPE containers with silica desiccants at 40°C/75% RH. The results of drug release investigations of pellets containing PEO, guaifenesin and GMS (formulation 1) are illustrated in Figure 5.4. The dissolution profiles of the stored pellets were compared to that of the unstored beads using a model independent approach to calculate difference and similarity

factors, also known as f_1 and f_2 values. Dissolution curves are considered equivalent when f_1 values are less than 15 and f_2 values are greater than 50 (Guidance 1997). The f_1 values calculated for the dissolution profiles of the 1 and 3 month samples were 11.1 and 14.7, while the f_2 values were 33.1 and 25.7, respectively. Thus, guaifenesin release rate decreased after as the 1 and 3 month accelerated stability studies since the similarity factors were not greater than 50.

Despite changes in the dissolution profile, the water content of pellets was not significantly influenced by the storage conditions as the pellets were stored in sealed HDPE containers with silica desiccants. The initial pellets exhibited a weight loss on drying of 0.51 ± 0.06%, while the weight loss on drying of beads stored for 1 or 3 months at 40°C/75% RH was 0.46 ± 0.08 and 0.48 ± 0.06%, respectively.

Stabilization of the drug release properties of polymeric matrices is challenging since such systems frequently exhibit changes in dimensional structure upon storage that can significantly decrease the drug release rate. This phenomenon is most frequently observed at storage conditions near or above the glass transition temperature of the matrix material, where stress relaxation and orientation of polymer chains is rapid (Omelczuk 1993).

Effective porosity is the space occupied by air inside a dosage form prior to drug dissolution, and porous systems usually exhibit faster drug release since there are more channels for water to enter and to dissolve the API. Tortuosity describes the directness of a path from the surface of a dosage form to an internal void. Diffusion pathways are more convoluted in systems with high tortuosity, thus hindering drug diffusion though the matrix pores. Several researchers have noted that decreases in drug release rate upon storage corresponded with

decreases in porosity and/or increases in tortuosity (Rubio 1994, Zhang 2001, Crowley 2002). The HME pellets containing guaifenesin and PEO did not exhibit changes in porosity or tortuosity as demonstrated in Table 5.3. These results are in line with the findings of previous researchers who have noted that melt-extruded matrix dosage forms do not exhibit significant changes in matrix structure upon storage since compression and intense mixing of molten materials during processing results in a product with low free volume (Kidokoro 2001).

Product crystallinity was studied to determine the morphological stability of the system. As seen in Figure 5.5, SEM analysis of pellet surfaces revealed crystal growth upon storage at accelerated conditions. Crystals were not visible initially on the pellet surface after thermal processing, but crystal growth increased with storage time as more significant morphological changes were observed with the 3 month sample. Additional studies were conducted to determine which formulation components recrystallized.

The X-ray diffraction profiles of the pellet components, physical blend and processed pellets are seen in Figure 5.6. The physical blend of materials exhibited crystallinity peaks characteristic of PEO at the 2-theta angles 19.1 and 23.4, while guaifenesin peaks were detected at 12.1, 13.6 and 20.8. After thermal processing, only the PEO peaks at 19.1 and 23.4 remained, but the peak intensity was significantly reduced. These findings indicated that guaifenesin existed as a solid solution or a solid amorphous embedding in the semi-crystalline carrier polymer. The intensity of the PEO peaks increased upon storage, and guaifenesin recrystallized as peaks were detected at the 2-theta angles 12.1, 13.6 and 20.8 in the 3 month stability sample. Thus, PEO crystallinity increased and guaifenesin

recrystallized upon storage at 40°C/75% RH in sealed HDPE containers with silica desiccants.

In addition to crystallization of PEO and guaifenesin, the adhesion behavior of HME beads changed after storage at accelerated conditions. During the initial dissolution investigations, melt-extruded pellets adhered individually to the wall of the glass dissolution vessels. The stability samples did not stick or agglomerate during storage, but the beads adhered to form a single mass during dissolution testing. This phenomenon explains the observed decrease in drug release rate after storage since the agglomerated pellets exhibited a reduced surface area to volume ratio when compared to the individual pellets. Previous researchers have noted that matrix geometry can significantly influence drug release rate from systems containing swellable polymers (Katzhendler 1997, Siepmann 2000).

Ethylcellulose is a water-insoluble excipient which controls drug release rate by modifying the size and length of diffusion pathways of matrix systems (Katikaneni 1995). The influence of ethylcellulose on the drug release properties of guaifenesin and PEO containing matrix pellets is illustrated in Figure 5.7. The percentage of guaifenesin released after dissolution testing for 1 h in pH 6.8 medium was reduced from 80 to 60% upon the addition of 15% ethylcellulose (formulation 2). Furthermore, the drug release properties of the pellets were stable after storage for 1 and 3 months at accelerated conditions. Although ethylcellulose containing pellets also exhibited recrystallization of guaifenesin and PEO during storage as detected by SEM and X-ray diffraction studies, the adhesion behavior of beads during dissolution testing did not change. The initial

and stored pellets agglomerated to form a single mass during dissolution investigations.

5.3.4 Film-coating of melt-extruded pellets

Eudragit® L 30 D-55 is an anionic copolymer of methacrylic acid and methacrylates used for enteric drug delivery applications since it solubilizes in aqueous media above pH 5.5. Thermally extruded pellets containing PEO, guaifenesin and GMS (formulation 1) were film-coated with 5, 10, 15 or 20% polymer weight gain, and sticking problems were not observed during processing despite the low melting point of the guaifenesin/PEO dispersion. Figure 5.8 shows that the process was efficient since all coating levels released less than 10% guaifenesin after 2 h in 0.1 N HCl, with no drug release detected from the pellets coated with 10, 15 or 20% polymer weight gain. Although a decrease in the drug release rate from uncoated pellets was observed, the drug release properties of melt-extruded pellets coated with Eudragit® L 30 D-55 were stable after storage for 1 and 3 months at 40C/75% RH in sealed HDPE containers with silica desiccants. Table 5.4 demonstrates the drug release properties of beads coated with 10% weight gain of polymer.

5.4 CONCLUSIONS

The calculation of Hansen solubility parameters was demonstrated to be a useful method for predicting the miscibility of drug/polymer blends used a novel melt-extrusion and spheronization process. The drug release properties of matrix beads containing PEO, guaifenesin and GMS were not stable upon storage at accelerated conditions although the water content and dimensional structure of pellets did not change. Despite miscibility of the drug/polymer blend, the pellets

were morphologically unstable since PEO and guaifenesin recrystallized upon storage as detected by SEM and X-ray diffraction studies. Furthermore, reduction in the drug release rate was contributed to agglomeration of pellets during dissolution testing. The addition of ethylcellulose to the extruded powder blend and film-coating with Eudragit® L 30 D-55 stabilized the drug release properties of the thermally processed pellets. Furthermore, film-coating was demonstrated to be an efficient process for providing melt-extruded beads with pH-dependent drug release properties despite the use of low melting point of thermal carriers.

5.5 REFERENCES

Andreola, F.; Leonelli; C.; Romagnoli, M. Techniques used to determine porosity. American Ceramic Society Bulletin. 2000, July, 49-52.

Breitenbach, J. Melt extrusion: from process to drug delivery technology. European Journal of Pharmaceutics and Biopharmaceutics. 2002, 54 (2), 107-117.

Breitenbach, J.; Mägerlein, M. Melt-extruded molecular dispersions. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 245-260.

Crowley, M.M.; Zhang, F.; Koleng, J.J.; McGinity, J.W. Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion. Biomaterials. 2002, 23, 4241-4248.

Crowley, M.C.; Schoeder, B.; Fredersdorf, A.; Obara, S.; Talarico, M.; Kucera, S.; McGinity, J.W. Physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablets prepared by direct compression and hot-melt extrusion. International Journal of Pharmaceutics. 2004, 269(2), 509-522.

Di Colo, G.; Burgalassi, S.; Chetoni, P.; Fiaschi, M.P; Zambito, Y.; Saettone, M.F. Gel-forming erodible inserts for ocular controlled delivery of ofloxacin. International Journal of Pharmaceutics. 2001, 215, 101-111.

Forster, A.H.; Hempenstall, J.; Rades, T. Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers. Journal of Pharmacy and Pharmacology. 2001, 53, 303–315.

Greenhalgh, D.; Williams, A.; Timmins, P.; York, P. Solubility parameters as predictors of miscibility in solid dispersions. Journal of Pharmaceutical Sciences. 1999, 88, 1182–1190.

Gruenhagen, H.H. Polymer/drug-melt extrusion: therapeutic and technological appeal. Pharmaceutical Technology Europe. 1996, 11, 22–27.

Guidance for industry: dissolution testing of immediate release solid oral dosage forms. 1997, http://www.fda.gov/cder/guidance/1713bp1.pdf (accessed June 2004).

Hancock, B.C.; Zografi, G. Characteristics and significance of the amorphous state in pharmaceutical systems. Journal of Pharmaceutical Sciences. 1997, 86, 1–12.

Katikaneni, P.R.; Upadrashta, S.M.; Rowlings, C.E.; Neau, S.H.; Hileman, G.A. Consolidation of ethylcellulose: effect of particle size, press speed, and lubricants. International Journal of Pharmaceutics. 1995, 117, 13–21.

Katzhendler, I.; Hoffman, A.; Goldberger, A.; Friedman, M. Modeling of drug release from erodible tablets. Journal of Pharmaceutical Sciences. 1997, 86 (1), 110-115.

Kidokoro, M.; McGinity, J.W. Properties of tablets containing granulations of ibuprofen and acrylic copolymer prepared by thermal processes. Pharmaceutical Development and Technology. 2001, 6, 263-275.

Omelczuk, M.O.; McGinity, J.W. The influence of thermal treatment on the physical-mechanical and dissolution properties of tablets containing poly(dl-lactic acid). Pharmaceutical Research. 1993, 10, 542-548.

Repka, M.A.; McGinity, J.W. Influence of Vitamin E TPGS on the properties of hydrophilic films produced by hot-melt extrusion. International Journal of Pharmaceutics. 2000, 202, 63-70.

Rubio, M.; Ghaly, E. In vitro release of acetaminophen from sodium alginate controlled release pellets. Drug Development and Industrial Pharmacy. 1994, 20, 1239-1251.

Siepmann, J.; Peppas, N.A. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advanced Drug Delivery Reviews. 2001, 48, 139-157.

Sinha, V.; Trehan, A. Biodegradable microspheres for protein delivery, Journal of Controlled Release. 2002, 90, 261-280.

Sood, A.; Panchagnula, R. Design of controlled release delivery systems using a modified pharmacokinetic approach: a case study for drugs having a short elimination half-life and a narrow therapeutic index. International Journal of Pharmaceutics. 2003, 261 (1-2), 27-41.

Suzuki, H.; Sunada, H. Influence of water-soluble polymers on the dissolution of nifedipine solid dispersions with combined carriers. Chemical and Pharmaceutical Bulletin. 1997, 45, 1688–1693.

Van Krevelen, D.W.; Hoftyzer, P.J. *Properties of Polymers*, 3rd Ed.; Elsevier: Amsterdam, 1990.

Varner, J. Descriptive fractography, ceramics and glasses. Engineered Materials Handbook. 1991, 4, 634-644.

Vogel, A.I.; Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. *Textbook of Practical Organic Chemistry*, 5th Ed.; Addison-Wesley: London, 1996.

Young, C.R.; Koleng, J.J.; McGinity, J.W. Production of spherical pellets by a hot-melt extrusion and spheronization process. International Journal of Pharmaceutics. 2002, 242, 87-92.

Young, C.R.; Koleng, J.J.; McGinity, J.W. Properties of drug-containing spherical pellets produced by a hot-melt extrusion and spheronization process. Journal of Microencapsulation. 2003, 20, 613-625.

Zhang, F.; McGinity, J.W. Properties of sustained release tablets prepared by hot-melt extrusion. Pharmaceutical Development and Technology. 1999, 4, 241–250.

Zhang, Y.E.; Tchao, R.; Schwartz, J.B. Effect of processing methods and heat treatment on the formation of wax matrix tablets for sustained drug release. Pharmaceutical Development and Technology. 2001, 6, 131-144.

Zhu, Y.; Shah, N.H.; Malick, A.W.; Infeld, M.H.; McGinity, J.W. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. International Journal of Pharmaceutics, 2002, 241(2), 301-310.

Table 5.1: Pellet formulations and functions of components.

COMPONENT	FUNCTION	FORMULATION (% W/W)	
		1	2
Guaifenesin	Model Drug	20	20
PEO (POLYOX™ Mw. 4 x 10^6)	Thermal Carrier	78	63
Ethylcellulose (Ethocel® 100FP)	Release Modifying Agent	0	15
GMS (Imwitor® 491)	Thermal Lubricant	2	2

Table 5.2: Hansen solubility parameters calculated using the group contribution method as described by Van Krevelen and Hoftyzer.

	δ_t	δ_d	δ_p	δ_h
Guaifenesin	25.85	18.88	5.57	16.76
PEO	22.87	17.78	11.11	9.13
	$\Delta\delta_t$(Guaifenesin - PEO) = 2.99 $MPa^{1/2}$			

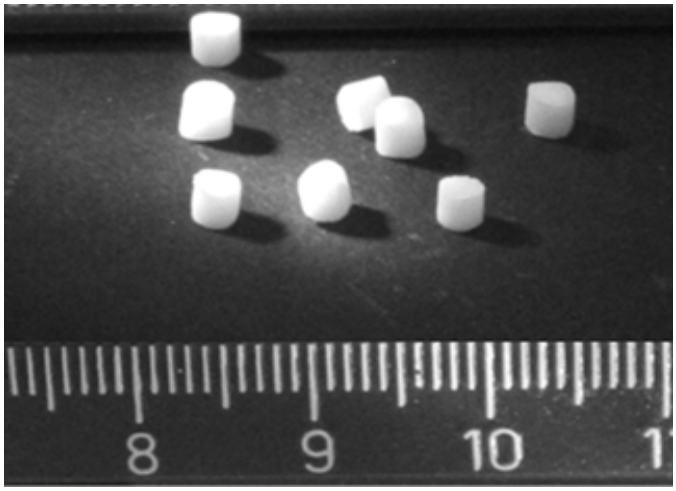
Table 5.3: Influence of storage time at 40°C/75% RH in sealed HDPE containers with silica desiccants on the porosity and tortuosity of melt-extruded pellets (n = 3).

SAMPLE	% EFFECTIVE POROSITY	TORTUOSITY
Initial	2.41 ± 0.33	156 ± 23
1 Month 40°C/75% RH	2.79 ± 0.57	179 ± 31
3 Months 40°C/75% RH	2.70 ± 0.75	164 ± 26

Table 5.4: Drug release properties of formulation 1 pellets coated with 10% weight gain of Eudragit® L 30 D-55. (*n* = 6, USP 27 Apparatus 2, Method A, 2 h in 750 mL of 0.1 N HCl followed by 6 h in 900 mL of pH 6.8 phosphate buffer, 37°C, 100 rpm).

SAMPLE	% DRUG RELEASED 2 HR IN 0.1N HCl	% DRUG RELEASED 1 HR pH 6.8 PBS
Initial	0	53.2
1 Month 40°C/75% RH	0	51.3
3 Months 40°C/75% RH	0	52.5

A.



B.

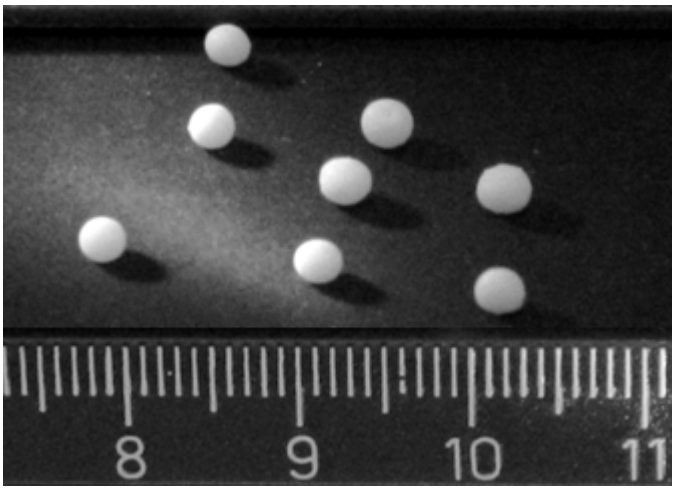


Figure 5.1: Pellets containing PEO, guaifenesin and GMS before and after spheronization for 15 min using a novel melt extrusion process.

Key: A. Cylindrical pellets before spheronization; B. Spherical pellets after spheronization.

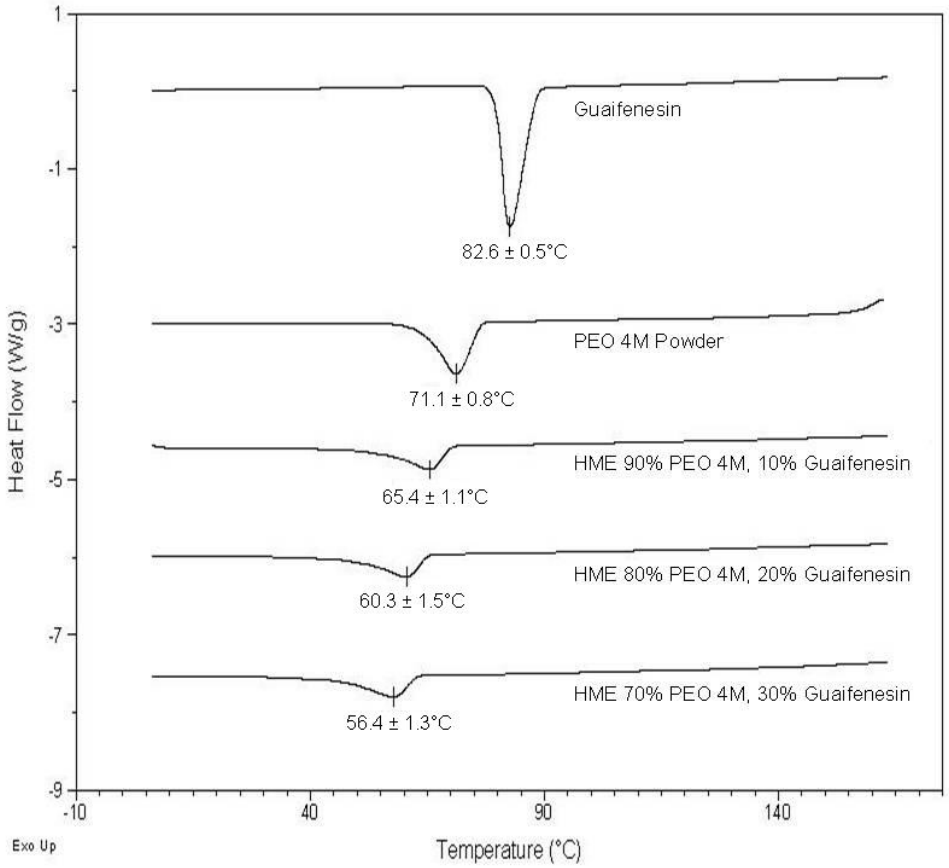


Figure 5.2: Thermal properties of guaifenesin, PEO (Mw. 4,000,000) and melt-extrudates of blends (n = 3).

Key: A. Guaifenesin; B. PEO; C. Extrudate—10% Guaifenesin, 90% PEO; D. Extrudate—20% Guaifenesin, 80% PEO; E. Extrudate—30% Guaifenesin, 70% PEO.

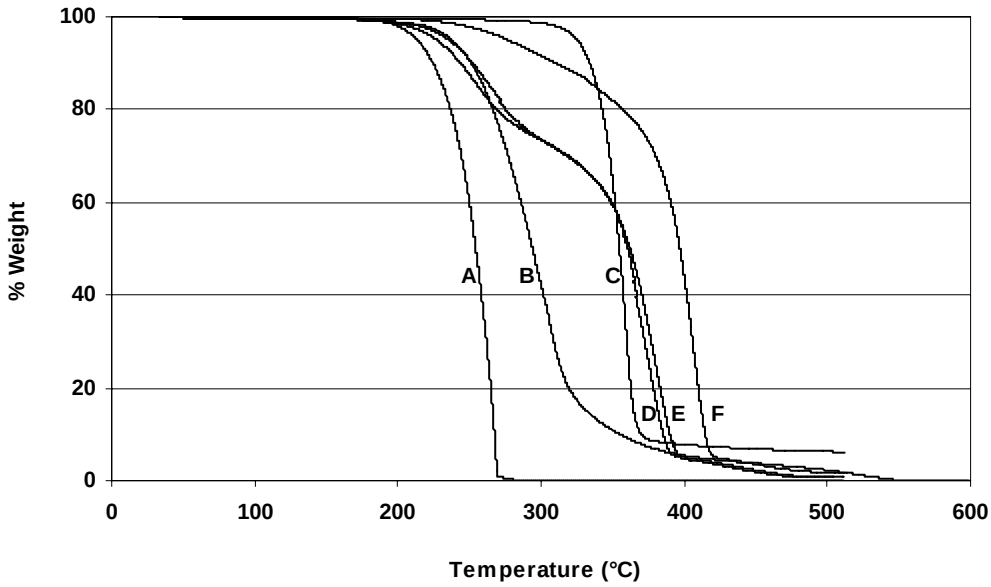


Figure 5.3: Thermal gravimetric analysis of pellet formulation components and physical blends prior to melt-processing.

Key: A. Guaifenesin; B. GMS; C. Ethylcellulose; D. Physical blend of formulation 1; E. Physical blend of formulation 2; F. PEO (Mw. 4,000,000).

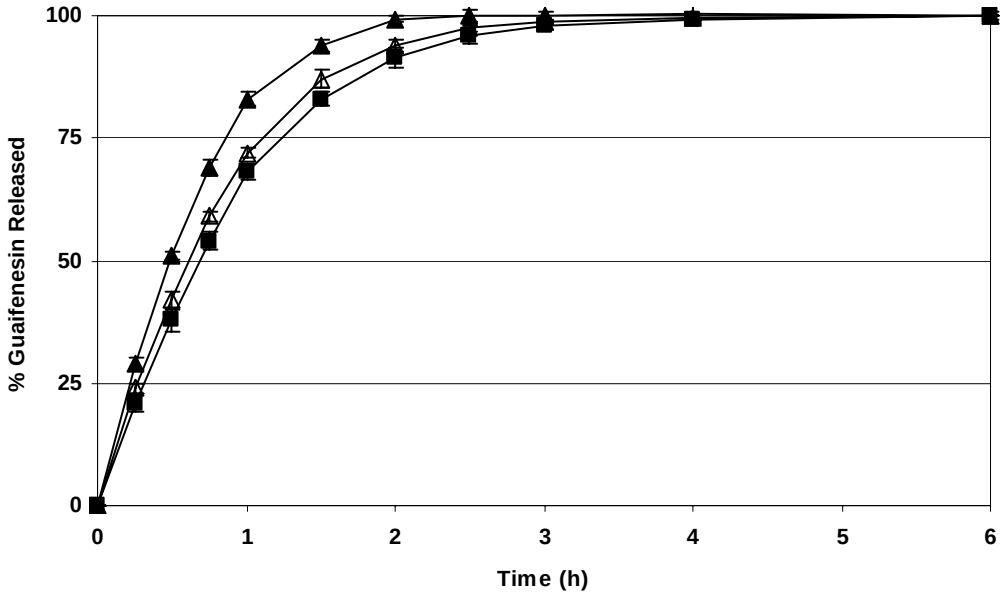
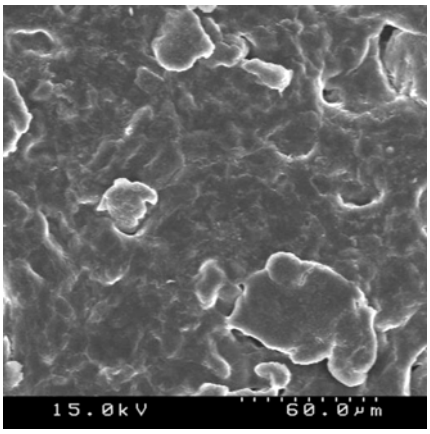


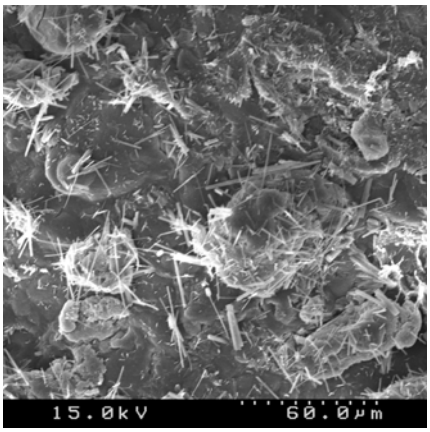
Figure 5.4: Stability of guaifenesin release rate from formulation 1 melt-extruded pellets upon storage at 40°C/75% RH in sealed HDPE containers with silica desiccants (n = 6, USP 27 Apparatus 2, 900 mL of 0.1 N HCl, 37°C, 100 rpm).

Key: ▲ Initial; △ 1 Month; ■ 3 Months.

A.



B.



C.

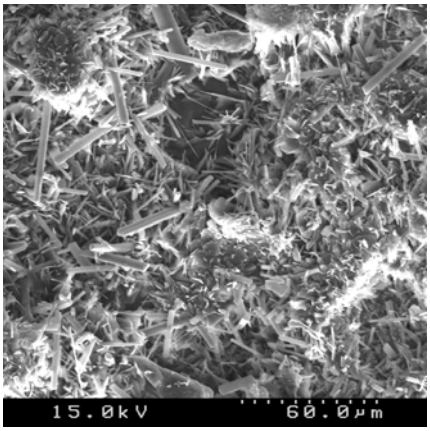


Figure 5.5: SEM analysis of the surface of spherical pellets upon storage at accelerated conditions in sealed HDPE containers with silica desiccants.

Key: A. Initial; B. 1 Month; C. 3 Months.

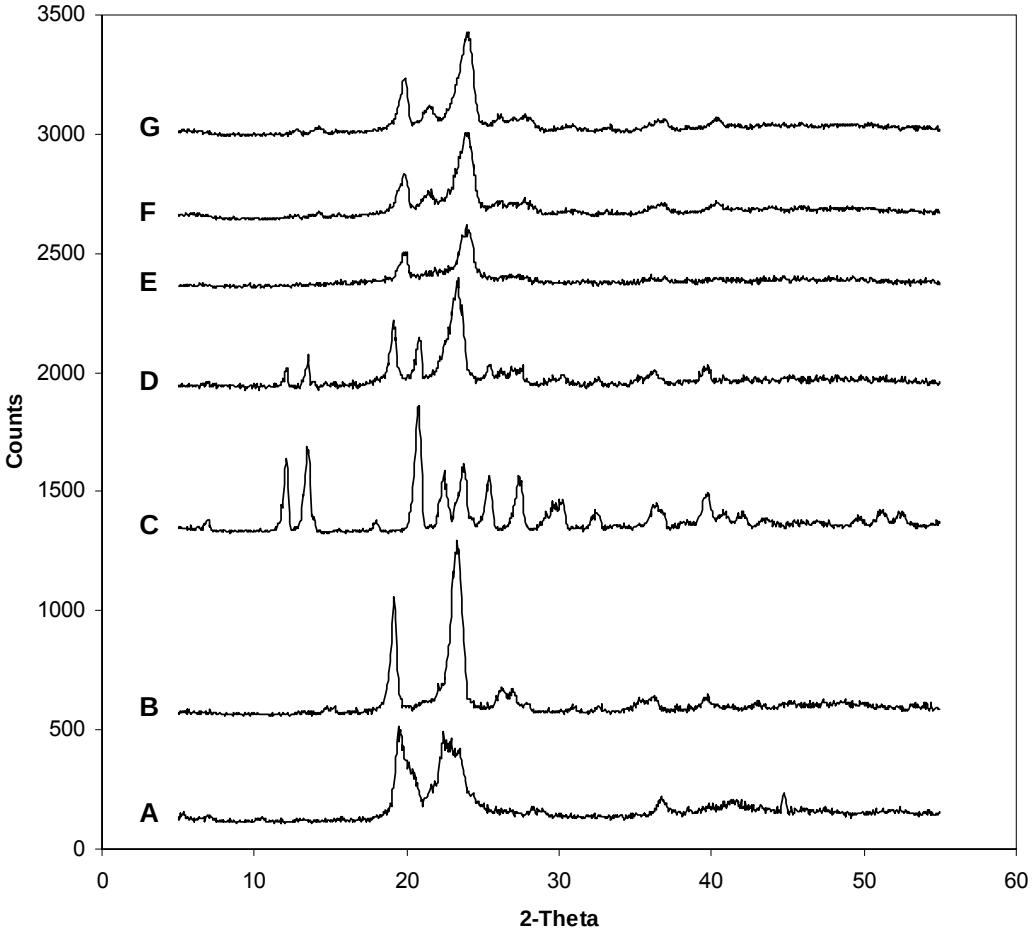


Figure 5.6: X-ray diffraction profiles of pellet formulation components and melt-extruded beads before and after storage at 40°C/75% RH in sealed HDPE containers with silica desiccants.

Key: A. GMS; B. PEO (Mw. 4,000,000); C. Guaifenesin; D. Powder blend; E. Initial beads; F. Beads after storage for 1 month; G. Beads after storage for 3 months.

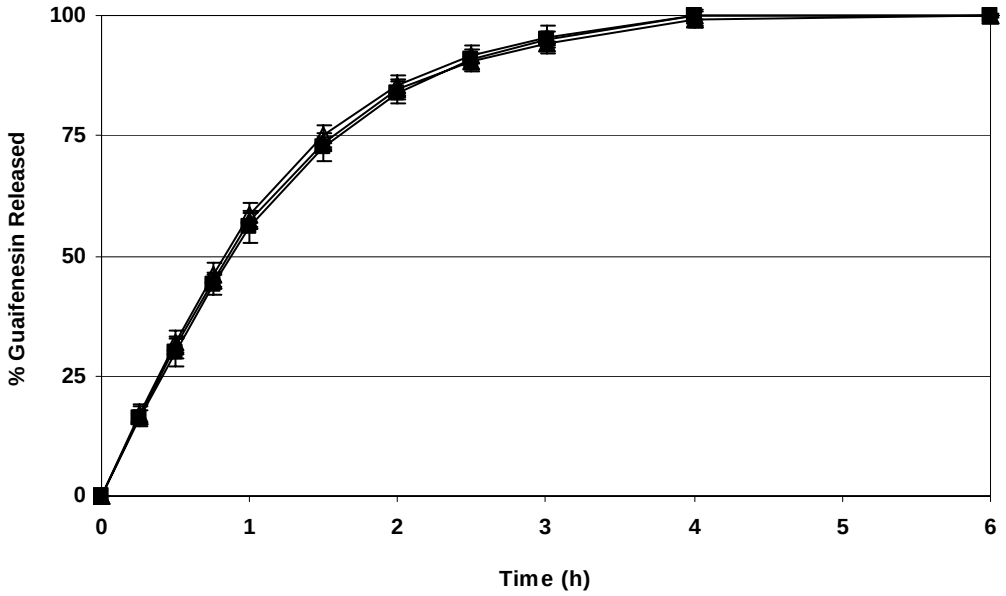


Figure 5.7: Stability of guaifenesin release rate from formulation 2 melt-extruded pellets containing ethyl cellulose upon storage at accelerated conditions in sealed HDPE containers with silica desiccants (n = 6, USP 27 Apparatus 2, Method A, 2 h in 750 mL of 0.1 N HCl followed by 6 h in 900 mL of pH 6.8 phosphate buffer, 37°C, 100 rpm).

Key: ▲ Initial; △ 1 Month; ■ 3 Months.

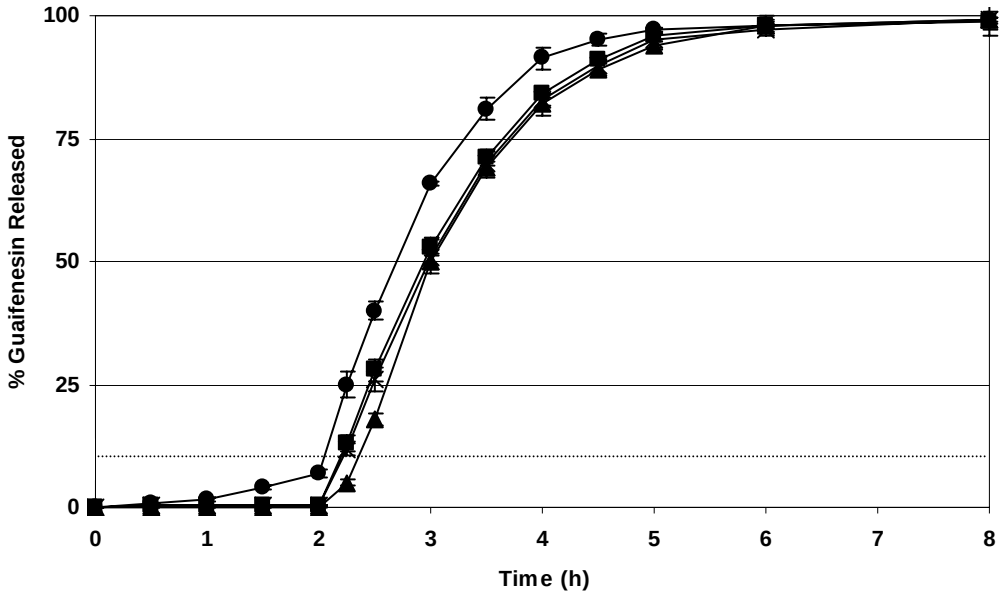


Figure 5.8: Influence of Eudragit® L 30 D-55 weight gain on the guaifenesin release profile of HME spherical pellets (n = 6, USP 27 Apparatus 2, Method A, 2 h in 750 mL of 0.1 N HCl followed by 6 h in 900 mL of pH 6.8 phosphate buffer, 37°C, 100 rpm).

Key: ● 5%; ■ 10%; ✕ 15%; ▲ 20%.

Chapter 6: Physicochemical characterization and mechanisms of release of theophylline from melt-extruded dosage forms based on a methacrylic acid copolymer

6.1 INTRODUCTION

Controlled delivery of bioactive agents is a major focus of pharmaceutical research since multiple dosing regimens often present problems with patient compliance, toxicity and therapeutic index (Sood 2003). Polymeric drug carrier systems have been widely studied to sustain, modify or target drug delivery.

Hot-melt extrusion (HME) of thermoplastic polymers have been used to produce a variety of controlled release dosage forms, including pellets, granules, tablets, suppositories, transdermal systems and ophthalmic inserts (Breitenbach 2002, McGinity 2003, Zhu 2002). Acryl-EZE® is a pre-mixed excipient blend optimized for film-coating that is based on the methacrylic acid copolymer Eudragit® L 100-55. Although researchers have studied the pH-dependent drug release properties of melt-extruded bead matrices containing the acrylic copolymer Eudragit® Preparation 4135 F (Young 2003), the thermal processing applications of Acryl-EZE® have not been investigated.

Mixtures of polymers, particularly cellulose ethers, are useful in regulating the drug release properties of dosage forms (Pose-Vilarnovo 2004). In tablet matrices, excipient mixtures not only modify drug release rate by producing gel barriers of varying consistency (Vazquez 1996), but they can also change the kinetics of drug release (Sung 1996). These effects are often due to interactions between the excipients that modify the microenvironment through

which the drug has to diffuse, particularly matrix viscosity and/or polarity (Alvarez-Lorenzo 1999, Alvarez-Lorenzo 2001).

Matrix systems containing hydrophilic polymers have been widely studied since drug release is controlled by a combination of polymer swelling, erosion and drug diffusion through the hydrated gel (Di Colo 2001). Methocel® (hydroxypropyl methylcellulose) polymers are linear non-ionic cellulose ethers commonly used in controlled release systems. The properties of HPMC matrices have been extensively studied regarding both mechanistic and technological factors involved in drug release (Ford 1991, Shah 1993, Mahaguna 2003). The Carbopols are anionic, high molecular weight polymers of acrylic acid. Several researchers have studied tablet formulations containing Carbopol® polymers to produce zero-order or near zero-order drug release kinetics (Capan 1989, Perez-Marcos 1991).

The purpose of the current study was to investigate the physicochemical properties of melt-extruded dosage forms based on Acryl-EZE® and to determine the influence of Methocel® K4M Premium and Carbopol® 974P on the mechanisms and kinetics of drug release. The physical and chemical stability of materials during thermal processing was studied using thermal gravimetric analysis and HPLC. The mechanism and kinetics of drug release were investigated using model fitting and matrix hydration and erosion studies.

6.2 MATERIALS AND METHODS

6.2.1 Materials

Acryl-EZE® was donated by Colorcon (Westpoint, PA). Anhydrous theophylline, anhydrous citric acid and glacial acidic acid were purchased from

Spectrum Chemical (Gardenia, CA). Carbopol® 974P (carbomer) and Methocel® K4M Premium (hydroxypropyl methylcellulose) were provided by Noveon (Cleveland, OH) and Dow Chemical (Midland, MI), respectively. All materials were passed through a 30 mesh screen prior to processing. Triethyl citrate (TEC) was donated by Moreflex (Greensboro, NC). Acetonitrile was purchased from EM Science (Gibbstown, NJ).

6.2.2 Thermal analysis of materials

Thermal gravimetric analysis (TGA) was performed using a Perkin-Elmer (Norwalk, CT) 7-series Thermogravimetrical Analyzer. The temperature ramp speed was set at 10°C/min, and the percentage weight loss of the samples was monitored from 25°C to 600°C. Volatiles were removed from samples by storing powders under vacuum with desiccants at 25°C for 72 h prior to thermal studies.

6.2.3 Melt-extrusion of dosage forms

The hot-melt extruded formulations consisted of theophylline, Acryl-EZE®, triethyl citrate and an optional gelling agent, Methocel® K4M Premium or Carbopol® 974P. The blends were mixed for 5 min in a ceramic mortar and pestle prior to addition of the liquid plasticizer TEC. After the plasticizer was geometrically added to the powder blends, the formulation was mixed for an additional 5 min. The blends were then extruded using a Randcastle Microtruder® RCP-0750 (Cedar Grove, NJ) single-screw extruder. The extruder was equipped with a Nitralloy 135M screw (3:1 compression ratio with flight configuration containing feed, compression and mixing sections). The temperature of the extruder barrel zones and die were set as follows using external temperature controllers: Zone 1 = 90°C, Zone 2 = 95°C, Zone 3 = 110°C

and Die = 115°C. A 6 mm cylindrical die and a screw speed of 20 rpm were employed for tablet production. The cylindrical extrudates were manually cut into tablets weighing approximately 250 mg.

A 1.2 mm cylindrical die and a screw speed of 10 rpm were employed for pellet production. After exiting the die, the polymeric strand was fed into a Randcastle Pelletizer RCP-2.0 and uniformly cut into cylindrical pellets. A 75 g sample of pellets was then transferred into a Caleva Model 120 Spheronizer (Dorset, England) that was maintained at 60-70°C using a Milwaukee™ Model 1220 (International Tool Corporation; Davie, FL) heat gun. A detailed description of the HME and spheronization process was reported earlier (Young 2002). The pellets were spheronized for approximately 15 min.

6.2.4 In vitro drug release studies

Dissolution studies were performed according to Apparatus 2 guidelines (paddle method) of USP 27 in a Van Kel VK7000 Dissolution Tester equipped with an auto sampler (Model VK 8000). The medium (900 mL) was maintained at 37°C and agitated at a speed of 50 rpm. Complete drug release was determined after mixing the vessel contents with a homogenizer for 5 min. The enteric dissolution properties of tablets were studied using dissolution testing for 2 h in 0.1 N HCl followed by testing in pH 6.8 phosphate buffered solution (PBS, 50 mM).

Samples were analyzed for drug content using a Waters HPLC system equipped with a photodiode array detector (Model 996) extracting at 281 nm. Samples were pre-filtered through a 0.2 μm membrane (Gelman Laboratory, GHP Acrodisc) to remove insoluble excipients. An auto sampler (Model 717plus) was used to inject 10 μL samples, and the data were collected and

integrated using Empower® Version 5.0 software. The column was an Alltech Inertsil™ ODS-3 3 μm, 150 x 4.6 mm, and the mobile phase contained a mixture of water:acetonitrile:glacial acetic acid in volume ratios of 845:150:5 and 1.156 g/L of sodium acetate trihydrate. The retention time of the theophylline was approximately 3.6 min. Linearity was demonstrated from 1 to 100 mg/μL ($r^2 \geq$ 0.998) and injection repeatability was approximately 1% relative standard deviation for 6 injections.

6.2.5 Analysis of Dissolution Data

The mechanism of drug release from cylindrical extrudates (0.6 cm x 6 cm) during dissolution investigations in 0.1 N HCl or pH 6.8 PBS was determined using equation 6.1, the Korsmeyer-Peppas model.

$$M_t/M_\infty = at^n \qquad \text{(Eq. 6.1)}$$

where M_t corresponds to the amount of drug released in time t, M_∞ is the total amount of drug that must be released at infinite time, a is a constant incorporating structural and geometric characteristics of the drug dosage form and n is the release exponent. Drug release data were employed for determination of the release exponent where $M_t/M_\infty \leq 0.6$.

The drug release kinetics of tablets (250 mg) during enteric dissolution testing were determined by finding the best fit of the dissolution data ($M_t/M_\infty \leq$ 0.85) to distinct models: zero-order (6.2), first-order (6.3), Hixson-Crowell (6.4) and Higuchi (6.5).

$$M_t = M_0 + K_0 t \qquad \text{(Eq. 6.2)}$$

$$\ln M_t = \ln M_0 + K_1 t \quad \text{(Eq. 6.3)}$$

$$M_t^{1/3} - M_0^{1/3} = K_S t \quad \text{(Eq. 6.4)}$$

$$M_t = K_H t^{1/2} \quad \text{(Eq. 6.5)}$$

where M_t is the amount of drug released at time t, M_0 is the total amount of drug in the solution at $t = 0$ (usually, $M_0 = 0$), and K_0, K_1, K_S and K_H are the kinetic rate constants for the zero-order, first-order, Hixson-Crowell and Higuchi models, respectively.

6.2.6 Hydration and erosion studies

The hydration and erosion of melt-extruded tablets (250 mg) were studied in 0.1 N HCl and pH 6.8 PBS under conditions identical to those described above for dissolution testing. Tablets were carefully removed from the dissolution vessel at predetermined time-points, and the wet weight was measured. The dosage forms were then dried at 55°C in a vacuum with desiccants for 7 days. The remaining dry weight was determined gravimetrically after equilibrating the dried tablets at 25°C in a vacuum with desiccants for 24 h. The percent hydration and mass remaining of tablets were determined gravimetrically according to the following equations:

$$\% \text{ Hydration} = 100(W_2 - W_3)/W_3 \quad \text{(Eq. 6.6)}$$

$$\% \text{ Mass Remaining} = 100(W_3/W_1) \quad \text{(Eq. 6.7)}$$

where W_1 is the initial dry weight of the tablet, W_2 is the wet weight and W_3 is the remaining dry weight after dissolution testing. Three tablets were used for each time-point.

6.3 RESULTS AND DISCUSSION

Matrix tablets based on Acryl-EZE® were melt-extruded using the formulations listed in Table 6.1. All formulations contained 20% theophylline based on the total formulation weight and 25% TEC based on the weight of Acryl-EZE®. Furthermore, the concentrations of the gelling agents studied were 2.5, 5 and 10%. The formulations containing Methocel® K4M required more drive amps and created higher pressures at the die when compared to the other blends. Furthermore, the mixture containing 10% Methocel® could not be extruded using the processing temperatures and plasticizer levels employed in the current study.

6.3.1 Thermal stability of materials

The thermal stability of materials was studied using TGA and HPLC. TGA is useful for determining processing temperatures since this method indicates thermal stability by measuring weight loss due to decomposition as a function of temperature. As seen in Figure 6.1, formulation components did not experience weight loss at the processing temperatures, which ranged from 90°C to 115°C. Acryl-EZE® exhibited a transition in the thermogram at approximately 170°C. A blend of Eudragit® L 100-55 and TEC also exhibited a weight loss at this temperature, whereas the weight of Eudragit® L 100-55 alone remained constant at temperatures below 200°C. Thus, the transition in the thermogram of Acryl-EZE® at 170°C was due to the loss of TEC. Although TGA provides a working temperature range, additional techniques are required to fully characterize the chemical stability of materials. The chemical stability of theophylline after HME was verified using a USP reversed-phase HPLC method.

6.3.2 In vitro drug release studies

Melt-extruded matrix tablets based on Acryl-EZE® exhibited pH-dependent theophylline release properties. As seen in Figure 6.2, melt-extruded tablets containing Acryl-EZE®, theophylline and TEC released approximately 10% drug after 2 h in 0.1 N HCl. Approximately 75% drug was released after 4 h, which included 2 h in 0.1 N HCl and 2 h in pH 6.8 PBS. The rapid drug release rate observed in the pH 6.8 medium was due to the pH-dependent solubility properties of the matrix polymer, Eudragit® L 100-55. The anionic methacrylic acid copolymer is widely employed for pH-dependent drug delivery applications since it solubilizes in aqueous media above pH 5.5.

It can also be seen in Figure 6.2 that Methocel® K4M Premium increased theophylline release in 0.1 N HCl. Since Eudragit® L 100-55 is insoluble in this medium, the hydrophilic polymer changed the drug release rate by increasing matrix permeability. Pollock and Balwinski (2000) studied Methocel® as a porosity modifier in an ethylcellulose compression coated system and noted that HPMC accelerated drug release by swelling and opening channels through which medium could enter the core. The current study also found that the amount of drug released during the first 2 h of dissolution testing increased with increasing HPMC concentration.

Although HPMC was a porosity modifier in 0.1 N HCl, the high molecular weight polymer decreased the rate of theophylline release in the pH 6.8 medium. Methocel® controlled drug diffusion by forming a gel matrix in the medium where Eudragit® L 100-55 was soluble. Additionally, the higher concentration of HPMC further decreased the rate of theophylline release due to

formation of a stronger gel matrix that was less libel to erosion (Gao 1996, Maggi 1999, Ranjani 1998).

The influence of Carbopol® 974P on the theophylline release rate is illustrated in Figure 6.3. Like HPMC, Carbopol® increased drug release in the pH 1.0 medium by increasing matrix permeability due to polymer swelling in the presence of water. However, this polymer more significantly reduced the rate of theophylline release in the pH 6.8 medium when compared to HPMC. The gel layer of Carbopol® containing matrix tablets is due to a chemically crosslinked network, while Methocel® containing tablets exhibit virtual crosslinking and gel formation as a result of polymer chain entanglement. Perez-Marcos (1994) and coworkers reported that Carbopol® 974 formed more viscous gels than Methocel® K4M when used at the same concentrations

The dissolution profiles of the tablets containing 5 or 10% Carbopol®, which exhibited complete drug release after approximately 14 h, were not significantly different as illustrated in Figure 6.3 (f_1 = 5, f_2 = 59). Generally, dissolution curves are considered equivalent when difference values (f_1) are less than 15 and similarity values (f_2) are greater than 50. However, the matrices containing 2.5% Carbopol® significantly extended the duration of drug release. Complete theophylline release was not obtained until approximately 20 h of dissolution testing.

The theophylline release profiles of Carbopol® containing tablets did not appear to be influenced by changes in the medium pH during enteric dissolution investigations. However, dissolution studies at pH 1.0 or 6.8 without media changes revealed that the matrix tablets exhibited pH-dependent drug release properties. The formulation containing 2.5% Carbopol® released approximately

68% theophylline after 10 h of enteric dissolution testing, while 52% and 83% drug were released after 10 h in the pH 1.0 and 6.8 media, respectively. Furthermore, concentration of the additive more significantly influenced drug release in 0.1 N HCl when compared to pH 6.8 PBS. Thus, the 2.5% Carbopol® tablets exhibited a more extended duration of theophylline release due to less significant changes in matrix permeability in the pH 1.0 medium.

As illustrated in Figure 6.4, Carbopol® 974P also significantly influenced the drug release properties of melt-extruded beads. Drug release rate increased in the pH 1.0 medium and decreased in the pH 6.8 medium upon addition of the polymer. However, unlike the findings of dissolution investigations of matrix tablets, Carbopol® only extended theophylline release for approximately 1 h longer than the melt-extruded beads without the polymeric additive. Furthermore, the 2.5% Carbopol® beads did not exhibit a significantly extended dissolution profile when compared to the beads containing 5 or 10% of the polymer. The rapid release of theophylline was due to the high surface area to volume ratio of beads. Other researchers have noted that matrix geometry significantly influences drug release rates from systems containing swellable polymers (Katzhendler 1997, Siepmann 2000). Matrix tablets were employed for model fitting and hydration/erosion studies since they exhibited a longer duration of drug release.

6.3.3 Mechanisms and kinetics of drug release

The mechanism of drug release from matrices containing swellable polymers is complex and not completely understood. Some systems may be classified as either purely diffusion or erosion controlled, while most systems exhibit a combination of these mechanisms (Siepmann 2001). The Korsmeyer-Peppas model is used to analyze drug release from pharmaceutical dosage forms

when the release mechanism is not well known or when more than one type of release phenomena is involved (Korsmeyer 1983). The exponent, termed the release exponent or n value, was studied by Peppas and coworkers (1985) to characterize different drug release mechanisms from thin films. They noted that profiles with $n = 0.5$ exhibited a drug release mechanism controlled by Fickian diffusion, while drug release rate was independent of time and controlled by a swelling mechanism when $n = 1$. A zero-order release mechanism is also known among polymer scientists as case-II transport. Values of n between 0.5 and 1.0 were regarded as an indicator for the superposition of both phenomena, and the drug release mechanism was termed anomalous (non-Fickian) transport.

The values of n for cylindrical systems were later determined (Ritger 1987): $n = 0.45$ (Fickian diffusion), $0.45 < n < 0.89$ (anomalous transport) and $n = 0.89$ (case-II transport). Furthermore, when determining the n exponent, only the portions of the release curve where $M_t/M_\infty \leq 0.6$ should be used. Another commonly overlooked requirement is that drug release occurs in a one-dimensional way, thus the length to width ratio of the device must be at least 10 (Costa 2001).

Drug release data from the dissolution investigations of cylindrical extrudates (0.6 cm x 6.0 cm) in either pH 1.0 or pH 6.8 medium were used for model fitting. As illustrated in Table 6.2, dissolution data fit the model well as a correlation coefficient (r^2) greater than 0.99 was obtained in all cases. The tablets without a swelling agent approached a release mechanism described by Fickian diffusion in 0.1 N HCl and exhibited primarily case-II transport in pH 6.8 PBS. The difference in release mechanism as a function of medium pH was a result of the pH-dependent solubility properties of Eudragit® L 100-55.

The tablets containing 2.5% Methocel® K4M or Carbopol® 974P also exhibited near Fickian diffusion controlled release in 0.1 N HCl, but an anomalous (non-Fickian) diffusional mechanism became apparent as the concentration of the gelling polymers increased. The additives resulted in an anomalous mechanism of drug release by increasing matrix permeability in the medium where Eudragit® L 100-55 was insoluble. Furthermore, the release exponent ranged form 0.64 to 0.80 in pH 6.8 PBS for all Methocel® and Carbopol® containing extrudates. Theophylline release from these matrices was controlled by a combination of polymer swelling, matrix erosion and diffusion of the drug in the hydrated polymer matrix.

The kinetics of drug release from Carbopol® containing tablets (250 mg) were analyzed using multiple drug release models as illustrated in Table 6.3. Only melt-extruded tablets containing the anionic swelling agent were studied since these dosage forms did not exhibit a biphasic drug release profile as a result of the media change during enteric dissolution testing. Tablets with 10% Carbopol® exhibited the highest correlation coefficient (r^2) with the zero-order model, while the formulations containing 2.5 or 5% of the polymer best fit the Higuchi model. Siepmann and Peppas (2001) noted that information from the Higuchi equation should be viewed with caution when studying devices containing swellable polymers since the model assumes constant diffusivities and dimensions of the devise during drug release. Carbopol® swells significantly during dissolution testing, and the diffusion coefficients of water and incorporated drugs are strongly concentration dependent (Siepmann 1999). Thus, swellable systems often exhibit square root of time kinetics although drug release is not necessarily based on a simple drug diffusion mechanism.

6.3.4 Hydration and erosion studies

The hydration and erosion of matrix tablets during dissolution investigations were studied to determine the influence of gelling agents on the mechanism of drug release from melt-extruded tablets. The results of these studies supported the findings of fitting to the Korsmeyer-Peppas model. Figure 6.5 illustrates the hydration, mass remaining and drug release profiles for tablets containing 2.5%. The results indicate that drug release was primarily diffusion controlled in 0.1 N HCl as there was minimal hydration or erosion of the matrix. When the medium was changed to pH 6.8 PBS, the diffusional exponent (*n*) increased to 0.80 as a result of significant tablet erosion. The low concentration of HPMC formed a gel with insufficient strength to maintain the matrix structure upon dissolution of Eudragit® L 100-55.

As illustrated in Figure 6.6, similar results were found for the 2.5% Carbopol® tablets in 0.1N HCl. Drug release was not significantly influenced by water uptake or tablet erosion. Furthermore, formation of a hydrogel in pH 6.8 PBS prevented significant matrix erosion and resulted in an anomalous (non-Fickian) drug release mechanism. The tablets absorbed approximately 1.5 times their weight in water after 4 h in pH 6.8 PBS. The percent water uptake and mass loss of these tablets were stable between the 8 and 20 h time points. Furthermore, investigators have noted that Carbopol® forms mechanically strong matrices at low concentrations due to the chemically crosslinked structure of the polymer that swells, but does not dissolve, in water (Perez-Marcos 1994).

6.3.5 Stability of drug release

Matrix tablets containing 2.5% Carbopol® were stored at 40°C/75% RH in induction sealed HDPE containers containing silica desiccants. Drug release rates from polymeric often decrease upon storage due to changes in the dimensional structure of the matrix (Omelczuk 1993, Zang 2001). As seen in Figure 6.7, the dissolution profiles of matrix tablets containing 2.5, 5 or 10% Carbopol® were stabled upon storage for 3 months at accelerated conditions. These results are in agreement with the findings of previous researchers who have noted that melt-extruded matrix dosage forms do not exhibit changes in matrix structure upon storage since compression and intense mixing of molten materials during processing results in a product with low free volume (Kidokoro 2001).

6.4 CONCLUSIONS

Although Acryl-EZE® is a pre-mixed excipient blend optimized for film-coating applications, the current study demonstrated the effectiveness of a melt-extrusion process to prepare controlled release systems based on Acryl-EZE®. The blend was stable during thermal processing, and resulted in dosage forms with pH-dependent dissolution properties.

Results also illustrated the influence of the physicochemical properties of gelling agents on the mechanism and kinetics of drug release from melt-extruded dosage forms. At low concentrations, Carbopol® 974P was more effective than Methocel® K4M Premium at controlling theophylline delivery in a medium where Eudragit® L 100-55 exhibited solubility. These findings were due to

chemical crosslinking nature of the polymeric additive which created a gel network that did not dissolve during dissolution investigations.

6.5 REFERENCES

Alvarez-Lorenzo, C.; Gómez-Amoza, J.L.; Martínez-Pacheco, R.; Souto, C.; Concheiro, A. Microviscosity of hydroxypropylcellulose gels as a basis for prediction of drug diffusion rates. International Journal of Pharmaceutics. 1999,180 (1), 91-103.

Alvarez-Lorenzo, C.; Duro, R.; Gómez-Amoza, J.L.; Martinez-Pacheco, R.; Souto, C.; Concheiro, A. Influence of polymer structure on the rheological behavior of hydroxypropylmethylcellulose-sodium carboxymethylcellulose dispersions. Colloid and Polymer Science. 2001, 579 (11), 1045–1057.

Breitenbach, J. Melt extrusion: from process to drug delivery technology. European Journal of Pharmaceutics and Biopharmaceutics. 2002, 54 (2), 107-117.

Capan, Y.; Senel, S.; Calis, S.T.; Hincal, A.A. Formulation and in-vivo evaluations on sustained release acetylsalicylic acid tablets. Pharmaceutical Industry. 1989, 51 (4), 443–448.

Costa, P.; Lobo, J.M.S. Modeling and comparison of dissolution profiles. European Journal of Pharmaceutical Sciences. 2001, 13 (2), 123-133.

Di Colo, G.; Burgalassi, S.; Chetoni, P.; Fiaschi, M.P, Zambito; Y.; Saettone, M.F. Gel-forming erodible inserts for ocular controlled delivery of ofloxacin. International Journal of Pharmaceutics. 2001, 215, 101-111.

Ford, J.L.; Mitchell, K.; Rowe, P.; Armstrong, D.J.; Elliott, P.N.C.; Rostron, C.; Hogan, J.E. Mathematical modeling of drug release from hydroxypropylmethylcellulose matrices: Effect of temperature. International Journal of Pharmaceutics. 1991, 71 (1-2), 95-104.

Gao, P.; Skoug, J.W.; Nixon, P.R.; Ju, T.R.; Stemm, N.L.; Sung, K.C. Swelling of hydroxypropyl methylcellulose matrix tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release. Journal of Pharmaceutical Sciences. 1996, 85 (7), 732-740.

Katzhendler, I., Hoffman, A.; Goldberger, A.; Friedman, M. Modeling of drug release from erodible tablets. Journal of Pharmaceutical Sciences. 1997, 86 (1) 10-115.

Kidokoro, M.; McGinity, J.W. Properties of tablets containing granulations of ibuprofen and acrylic copolymer prepared by thermal processes. Pharmaceutical Development and Technology. 2001, 6, 263-275.

Korsmeyer, R.W.; Gurny, R.; Doelker, E.M.; Buri, P.; Peppas, N.A. Mechanism of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics. 1983, 15 (1), 25–35.

Maggi, L.; Evelyn, O.M.; Torre, M.L.; Conte, U. Formulation of biphasic release tablets containing slightly soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics. 1999, 48 (1), 37-42.

Mahaguna, V.; Talbert, R.L.; Peters, J.I.; Adams, S.; Reynolds, T.D.; Lam, F.Y.W.; Williams, R.O., III. Influence of hydroxypropyl methylcellulose polymer on in vitro and in vivo performance of controlled release tablets containing alprazolam. European Journal of Pharmaceutics and Biopharmaceutics. 2003, 56 (3), 101-108.

McGinity, J.W.; Zhang, F. Melt-extruded controlled-release dosage forms. In Pharmaceutical Extrusion Technology, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 183-208.

Nellore, R.V.; Gurvinder, S.R.; Hussain, A.S.; Tillman, L.G.; Augsburger, L.L., Development of metoprolol tartrate extended-release matrix tablet formulations for regulatory policy consideration. Journal of Controlled Release. 1998, 50 (1-3), 247-256.

Omelczuk, M.O.; McGinity, J.W. The influence of thermal treatment on the physical-mechanical and dissolution properties of tablets containing poly(dl-lactic acid). Pharmaceutical Research. 1993, 10, 542-548.

Peppas, N.A. Analysis of Fickian and non-Fickian drug release from polymers. Pharmceutica Acta Helvetiae. 1985, 60 (4), 110–111.

Perez-Marcos, B.; Gutierrez, C.; Gomez-Amoza, J.L.; Rartinez-Pacheco, R.; Souto, C.; Concherio, A. Usefulness of certain varieties of Carbomer in the formulation of hydrophilic furosemide matrices. International Journal of Pharmaceutics. 1991, 67 (2), 113–121.

Perez-Marcos, B.; Ford, J.L.; Armstrong, D.J.; Elliott, P.N.C.; Rostron, C.; Hogan, J.E. Release of propranolol hydrochloride from matrix tablets containing hydroxypropylmethylcellulose K4M and carbopol 974. International Journal of Pharmaceutics. 1994, 111 (3), 251-259.

Pollock, D.K.; Balwinski, K.M. The utility of hypromellose as a porosity modifier in an ethylcellulose compression coating. Proceedings of the 27th International Symposium on Controlled Release of Bioactive Materials, Paris, France, July 7- 13, 2000.

Pose-Vilarnovo, B.; Rodríguez-Tenreiro, C.; Santos, J.F.; Vázquez-Doval, J.; Concheiro, A.; Alvarez-Lorenzo, C.; Torres-Labandeira, J.L. Modulating drug release with cyclodextrins in hydroxypropyl methylcellulose gels and tablets. Journal of Controlled Release. 2004, 94 (2-3), 351-363.

Ritger, P.L.; Peppas, N.A. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. Journal of Controlled Release. 1987, 5 (1), 37–42.

Shah, N.; Zhang, G.; Apelian, V.; Zheng, F.; Infield, M.H.; Mallick, A.W. Prediction of drug release from hydroxypropyl methylcellulose (HPMC) matrices: effect of polymer concentration. Pharmaceutical Research. 1993, 10 (11), 1693–1695.

Siepmann, J.; Podual, K.; Sriwongjanya, M.; Peppas, N.A.; Bodmeier, R. A new model describing the swelling and drug release kinetics from hydroxypropyl methylcellulose tablets. Journal of Pharmaceutical Sciences. 1999, 88 (1), 65-72.

Siepmann, J.; Kranz, H.; Peppas, N.A.; Bodmeier, R. Calculation of the required size and shape of hydroxypropyl methylcellulose matrices to achieve desired drug release profiles. International Journal of Pharmaceutics. 2000, 201 (2), 151-164.

Siepmann, J.; Peppas, N.A. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advanced Drug Delivery Reviews. 2001, 48 (2-3), 139-157.

Sood, A.; Panchagnula, R. Design of controlled release delivery systems using a modified pharmacokinetic approach: a case study for drugs having a short elimination half-life and a narrow therapeutic index. International Journal of Pharmaceutics. 2003, 261 (1-2), 27-41.

Sung, K.C.; Nixon, P.R.; Skoug, J.W.; Ju, T.R.; Gau, P.; Topp, E.M.; Patel, M.V. Effect of formulation variables on drug and polymer release form HPMC-based matrix tablets. International Journal of Pharmaceutics. 1996, 142 (1), 53–60.

Vazquez, M.J.; Casalderrey, M.; Duro, R.; Gomez-Amoza, J.L.; Martinez-Pacheco, R., Souto, C.; Concheiro, A., Atenolol release from hydrophylic matrix tablets with hydroxypropylmethyl cellulose (HPMC) mixtures as gelling agent: effects of the viscosity of the HPMC mixture. European Journal of Pharmaceutical Sciences. 1996, 4 (1), 39–48.

Young, C.R.; Koleng, J.J.; McGinity, J.W. Production of spherical pellets by a hot-melt extrusion and spheronization process. International Journal of Pharmaceutics. 2002, 242 (1-2), 87-92.

Young, C.R.; Koleng, J.J.; McGinity, J.W. Properties of drug-containing spherical pellets produced by a hot-melt extrusion and spheronization process. Journal of Microencapsulation. 2003, 20 (5), 613-625.

Zhang, Y.E.; Tchao, R.; Schwartz, J.B. Effect of processing methods and heat treatment on the formation of wax matrix tablets for sustained drug release. Pharmaceutical Development and Technology. 2001, 6, 131-144.

Zhu, Y.; Shah, N.H.; Malick, A.W.; Infeld, M.H.; McGinity, J.W. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. International Journal of Pharmaceutics. 2002, 241 (2), 301-310.

Table 6.1: Percent compositions of formulations for melt-extrusion.

COMPONENT	FORMULATION					
	1	2	3	4	5	6
Theophylline	20	20	20	20	20	20
Acryl-EZE	64	62	60	62	60	56
TEC	16	15.5	15	15.5	15	14
Methocel K4M Premium	-	2.5	5	-	-	-
Carbopol 974P	-	-	-	2.5	5	10

Table 6.2: Korsmeyer-Peppas model fitting of dissolution data from cylindrical melt-extrudates (paddle method, 900 mL, 37°C, 50 rpm, n = 6).

Percent Additive	0.1 N HCl		pH 6.8 PBS	
	r^2	n	r^2	n
0	0.9995	0.46	0.9987	0.87
Methocel K4M				
2.5	0.9987	0.49	0.9997	0.80
5	0.9997	0.55	0.9993	0.72
Carbopol 974P				
2.5	0.9985	0.51	0.9992	0.60
5	0.9970	0.53	0.9996	0.61
10	0.9973	0.54	0.9994	0.64

Table 6.3: Model fitting of drug release data from enteric dissolution investigations of Carbopol containing tablets (paddle method, 2 h in 0.1 N HCl followed by 8 h in pH 6.8 phosphate buffer, 900 mL, 37°C, 50 rpm, $n = 6$).

Percent Carbopol 974P	Zero-Order		First-Order		Hixson-Crowell		Higuchi	
	r^2	K_0	r^2	K_1	r^2	K_S	r^2	K_H
2.5	0.9844	2.87	0.8275	0.18	0.9015	0.14	0.9933	12.31
5	0.9884	3.49	0.8418	0.19	0.9083	0.16	0.9928	13.94
10	0.9917	3.86	0.8468	0.23	0.9175	0.19	0.9899	14.21

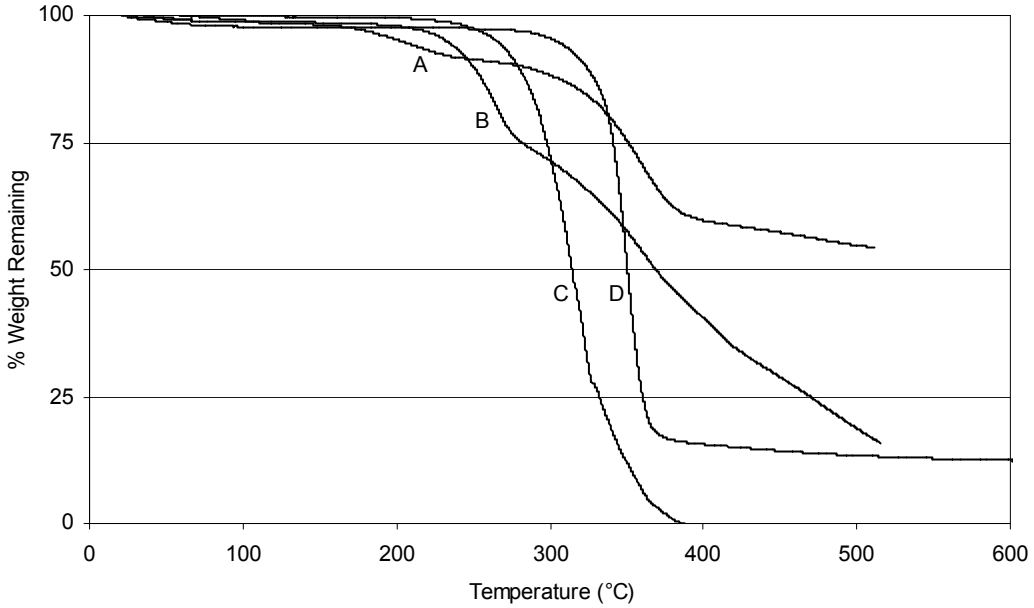


Figure 6.1: Thermal gravimetric analysis of formulation components.

Key: A. Acryl-EZE®; B. Carbopol® 974P; C. Theophylline; D. Methocel® K4M Premium.

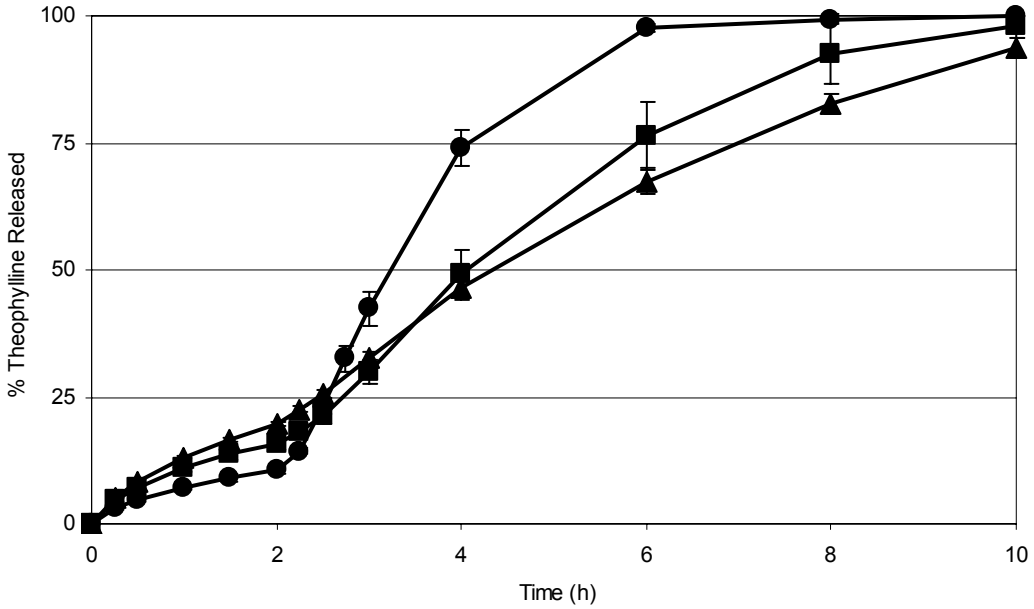


Figure 6.2: Influence of Methocel® K4M Premium on the theophylline release properties of melt-extruded Acryl-EZE® tablets (paddle method, 2 h in 0.1 N HCl followed by 8 h in pH 6.8 phosphate buffer, 900 mL, 37°C, 50 rpm, $n = 6$).

Key: ● 0%; ■ 2.5%; ▲ 5%.

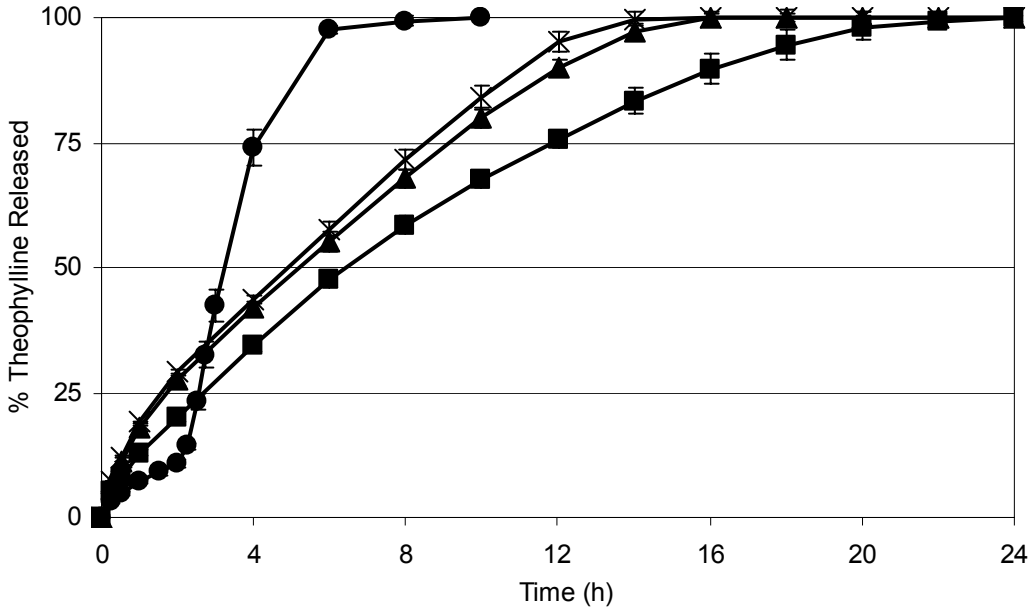


Figure 6.3: Influence of Carbopol® 974P on the theophylline release properties of melt-extruded Acryl-EZE® tablets (paddle method, 2 h in 0.1 N HCl followed by 22 h in pH 6.8 phosphate buffer 900 mL, 37°C, 50 rpm, $n = 6$).

Key: ● 0%; ■ 2.5%; ▲ 5%; ✕ 10%.

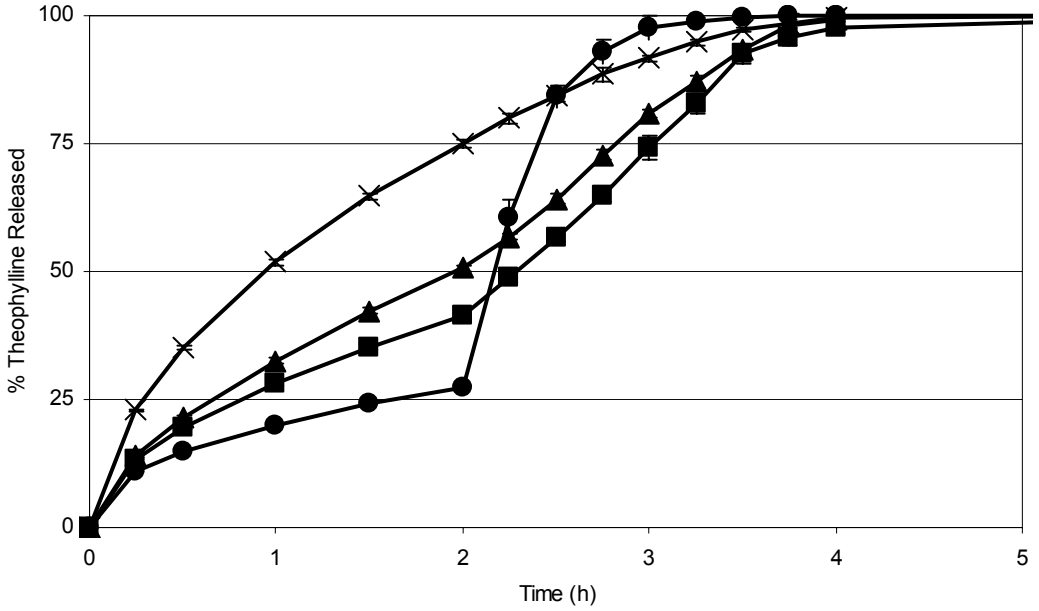


Figure 6.4: Influence of Carbopol® 974P on the theophylline release properties of melt-extruded Acryl-EZE® beads (paddle method, 2 h in 0.1 N HCl followed by 3 h in pH 6.8 phosphate buffer, 900 mL, 37°C, 50 rpm, $n = 6$).

Key: ● 0%; ■ 2.5%; ▲ 5%; ✕ 10%.

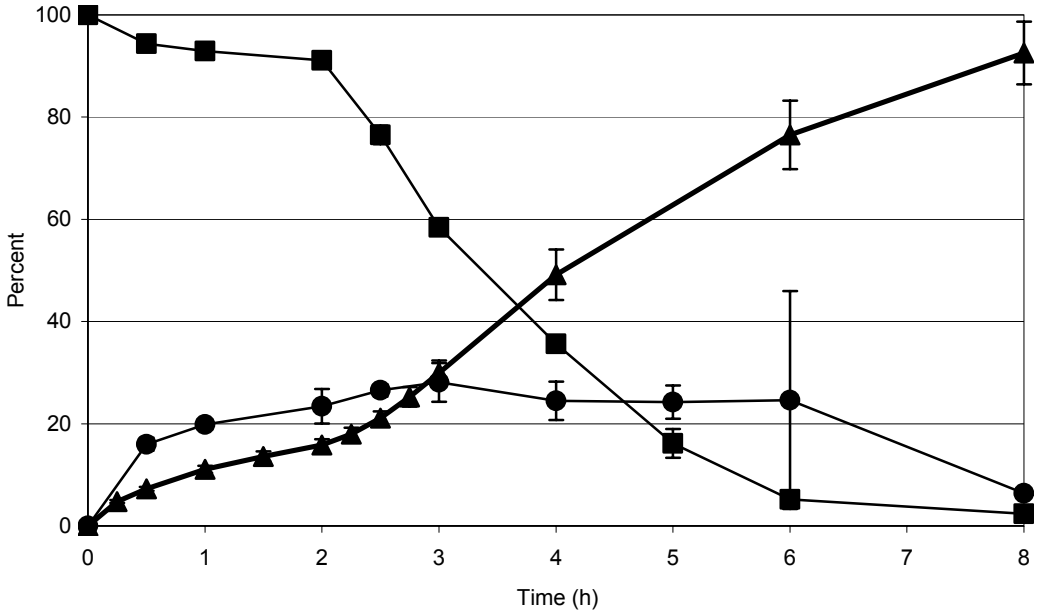


Figure 6.5: Influence of 2.5% Methocel® K4M Premium on the hydration, erosion and drug release properties of melt-extruded Acryl-EZE® tablets (paddle method, 2 h in 0.1 N HCl followed by 6 h in pH 6.8 phosphate buffer, 900 mL, 37°C, 50 rpm, Hydration/Erosion: $n = 3$, Drug Release: $n = 6$).

Key: ● Hydration; ■ Mass Remaining; ▲ Theophylline Released.

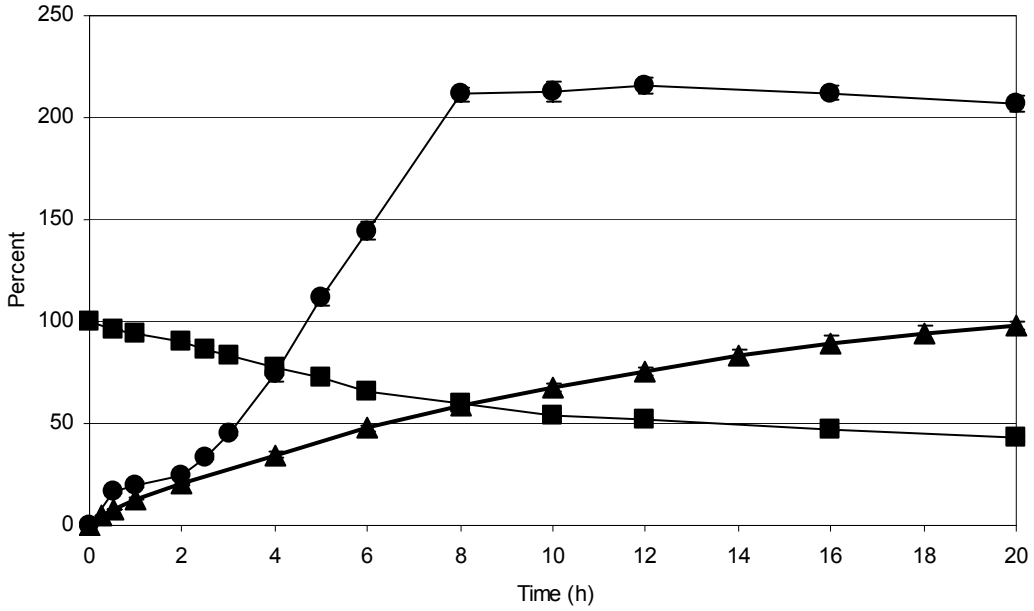


Figure 6.6: Influence of 2.5% Carbopol® 974P on the hydration, erosion and drug release properties of melt-extruded Acryl-EZE® tablets (paddle method, 2 h in 0.1 N HCl followed by 18 h in pH 6.8 phosphate buffer, 900 mL, 37°C, 50 rpm, Hydration/Erosion: $n = 3$, Drug Release: $n = 6$).

Key: ● Hydration; ■ Mass Remaining; ▲ Theophylline Released.

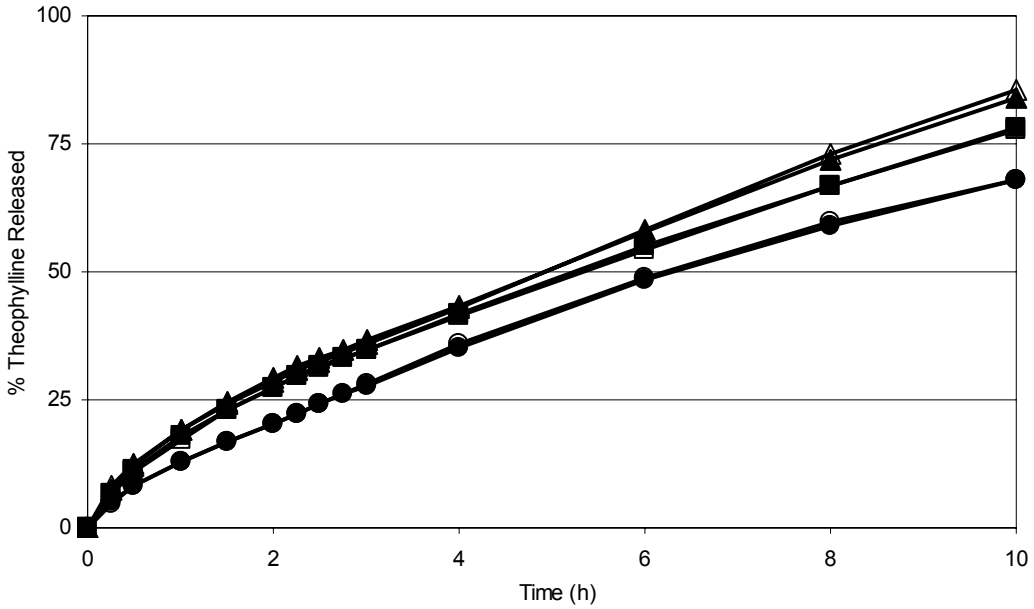


Figure 6.7: Stability of theophylline release rate from melt-extruded Acryl-EZE® tablets containing Carbopol® 974P upon storage for 3 months at 40°C/75% RH in induction sealed HDPE containers with silica desiccant (paddle method, 2 h in 0.1 N HCl followed by 8 h in pH 6.8 phosphate buffer, 900 mL, 37°C, 50 rpm, $n = 6$).

Key: ● 2.5%, initial; ○2.5%, stored; ■ 5%, initial; □ 5%, stored; ▲ 10%, initial; △10%, stored.

Bibliography

Aitken-Nichol, C.; Zhang, F.; McGinity, J.W. Hot-melt extrusion of acrylic films. Pharmaceutical Research. 1996, 3, 804–808.

Alvarez-Lorenzo, C.; Gómez-Amoza, J.L.; Martínez-Pacheco, R.; Souto, C.; Concheiro, A. Microviscosity of hydroxypropylcellulose gels as a basis for prediction of drug diffusion rates. International Journal of Pharmaceutics. 1999,180 (1), 91-103.

Alvarez-Lorenzo, C.; Duro, R.; Gómez-Amoza, J.L.; Martinez-Pacheco, R.; Souto, C.; Concheiro, A. Influence of polymer structure on the rheological behavior of hydroxypropylmethylcellulose-sodium carboxymethylcellulose dispersions. Colloid and Polymer Science. 2001, 579 (11), 1045–1057.

Andersson, M.; Holmquist, B.; Lindquist, J.; Nilsson, O.; Wahlund, K. Analysis of film coating thickness and surface area of pharmaceutical pellets using fluorescence microscopy and image analysis. Journal of Pharmaceutical and Biomedical Analysis. 2000, 22, 325-339.

Andreola, F.; Leonelli, C.; Romagnoli, M. Techniques used to determine porosity. American Ceramic Society Bulletin. 2000, July, 49-52.

Bechard, S.; Leroux, J. Coated palletized dosage form: effect of compaction on drug release. Drug Development and Industrial Pharmacy. 1992, 18 (Mar), 1927-1944.

Beckert, T.; Lehmann, K.; Schmidt, P. Compression of enteric-coated pellets to disintegrating tablets. International Journal of Pharmaceutics. 1996, 43 (1), 13-23.

Berner, B. and Dinh, S. Fundamental concepts in controlled release. In *Treatise on Controlled Drug Delivery*. Kydonieus, A., Ed.; Marcel Dekker: New York, 1992; 1-5.

Bianchini, R.; Bruni, G.; Gazzaniga, A; Vecchio, C. Influence of extrusion-spheronization on the physical properties of D-indobufen pellets containing pH adjusters. Drug Development and Industrial Pharmacy 1992, 18, 1485-1503.

Billa, N.; Yuen, K.; Peh, K. Diclofenac release from Eudragit®-containing matrices and effects of thermal treatment. Drug Development and Industrial Pharmacy. 1998, 24, 45-50.

Bloch, D.W.; Speiser, P.P. Solid dispersions—fundamentals and examples. Pharmaceutica Acta Helvetiae. 1987, 62, 23-27.

Bodmeier, R.; Paeraakul, O. Suspensions and dispersible dosage forms of multiparticulates. In *Multiparticulate Oral Delivery*, 1st Ed.; Ghebre-Sellassie, I., Ed.; Marcel Dekker: New York, 1994; Vol. 65, 143-158.

Bodmeier, R. Tableting of coated pellets. European Journal of Pharmaceutics and Biopharmaceutics. 1997, 43 (1), 1-8.

Breitenbach, J. Melt extrusion: from process to drug delivery technology. European Journal of Pharmaceutics and Biopharmaceutics. 2002, 54 (2), 107-117.

Breitenbach, J.; Mägerlein, M. Melt-extruded molecular dispersions. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 245-260.

Cao, Q.-R.; Choi, H.-G.; Kim, D.-C.; Lee, B.-J. Release behavior and photo-image of nifedipine tablet coated with high viscosity grade hydroxypropylmethylcellulose: effect of coating conditions. International Journal of Pharmaceutics. 2004, 274 (1-2), 107-117.

Capan, Y.; Senel, S.; Calis, S.T.; Hincal, A.A. Formulation and in-vivo evaluations on sustained release acetylsalicylic acid tablets. Pharmaceutical Industry. 1989, 51 (4), 443–448.

Case, C.C. Melt pelletization. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 99-110.

Chambliss, W.G. Conventional and specialized coating pans. In *Pharmaceutical Pelletization Technology*, 1st Ed; Ghebre-Sellassie, I., Ed.; Marcel Dekker: New York, 1989; Vol. 37, 15-38.

Chiou, W.; Riegelman, S. Pharmaceutical applications of solid dispersion systems. Journal of Pharmaceutical Sciences. 1971, 60, 1281-1301.

Chopra, R.; Alderborn, G.; Podczeck, F.; Newton, J.M. The influence of pellet shape and surface properties on the drug release from uncoated and coated pellets. International Journal of Pharmaceutics. 2002, 239, 171-178.

Chung, C.I. *Extrusion of Polymers: Theory and Practice*, 1st Ed.; Hanser: New York, 2000; 1-50.

Conine, J.W.; Hadley, H.R. Preparation of small solid pharmaceutical spheres. Drug & Cosmetic Industry. 1970, 106, 38-41.

Costa, P.; Lobo, J.M.S. Modeling and comparison of dissolution profiles. European Journal of Pharmaceutical Sciences. 2001, 13 (2), 123-133.

Crowley, M.M.; Zhang, F.; Koleng, J.J.; McGinity, J.W. Stability of polyethylene oxide in matrix tablets prepared by hot-melt extrusion. Biomaterials. 2002, 23, 4241-4248.

Crowley, M.C.; Schroeder, B.; Fredersdorf, A.; Obara, S.; Talarico, M.; Kucera, S.; McGinity, J.W. Physicochemical properties and mechanism of drug release from ethyl cellulose matrix tablets prepared by direct compression and hot-melt extrusion. International Journal of Pharmaceutics. 2004, 269(2), 509-522.

Cuff, G.; Raouf, F. A preliminary evaluation of injection molding as a technology to produce tablets. Pharmaceutical Technology. 1998, 22 (6), 97-106.

Di Colo, G.; Burgalassi, S.; Chetoni, P.; Fiaschi, M.P, Zambito; Y.; Saettone, M.F. Gel-forming erodible inserts for ocular controlled delivery of ofloxacin. International Journal of Pharmaceutics. 2001, 215, 101-111.

Doherty, C.; York, P.J. Evidence for solid- and liquid-state interaction in a furosemide-polyvinylpyrrolidone solid dispersion. Pharmaceutical Sciences. 1987, 76, 731-737.

Dyar, S.C.; Mollan, M. Melt-extruded particulate dispersions. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 261-276.

Erkoboni, D.F. Extrusion/Spheronization. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 277-322.

Follonier, N.; Doelker, E.; Cole, E. Evaluation of hot-melt extrusion as a new technique for the production of polymer based pellets for sustained release capsules containing high loading of freely soluble drugs. Drug Development and Industrial Pharmacy. 1994, 20, 1323–1339.

Follonier, N.; Doelker, E.; Cole, E.T. Various Ways of Modulating the Release of Diltiazem Hydrochloride from Hot-Melt Extruded Sustained-Release

Pellets Prepared Using Polymeric Materials. Journal of Controlled Release. 1995, 36(3), 243-250.

Ford, J.L.; Mitchell, K.; Rowe, P.; Armstrong, D.J.; Elliott, P.N.C.; Rostron, C.; Hogan, J.E. Mathematical modeling of drug release from hydroxypropylmethylcellulose matrices: Effect of temperature. International Journal of Pharmaceutics. 1991, 71 (1-2), 95-104.

Forster, A.H.; Hempenstall, J.; Rades, T. Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers. Journal of Pharmacy and Pharmacology. 2001, 53, 303–315.

Foster, T.; Parrott, E. Release of highly water-soluble medicinal compounds from inert, heterogeneous matrixes. II: melt. Journal of Pharmaceutical Sciences. 1990, 79, 938-942.

Gandhi, R.; Kaul; C.L.; Panchagnula, R. Extrusion and spheronization in the development of oral controlled-release dosage forms. Pharmaceutical Science and Technology Today. 1999, 2 (4), 160-170.

Gao, P.; Skoug, J.W.; Nixon, P.R.; Ju, T.R.; Stemm, N.L.; Sung, K.C. Swelling of hydroxypropyl methylcellulose matrix tablets. 2. Mechanistic study of the influence of formulation variables on matrix performance and drug release. Journal of Pharmaceutical Sciences. 1996, 85 (7), 732-740.

Ghali, E.S.; Klinger, G.H.; Schwartz, J.B. Thermal treatment of beads with wax for controlled release. Drug Development and Industrial Pharmacy. 1989, 15, 1311-1328.

Ghebre-Sellassie, I. Pellets: a general overview. In *Pharmaceutical Pelletization Technology*, 1st Ed; Ghebre-Sellassie, I., Ed.; Marcel Dekker: New York, 1989; Vol. 37, 1-13.

Goskonda, S.R; Upadrashta, S.M. Avicel RC-591/chitosan beads by extrusion/spheronization technology. Drug Development and Industrial Pharmacy. 1993, 19, 815-927.

Greenhalgh, D.; Williams, A.; Timmins, P.; York, P. Solubility parameters as predictors of miscibility in solid dispersions. Journal of Pharmaceutical Sciences. 1999, 88, 1182–1190.

Gruenhagen, H.H. Polymer/drug-melt extrusion: therapeutic and technological appeal. Pharmaceutical Technology Europe. 1996, 11, 22–27.

Guidance for industry: dissolution testing of immediate release solid oral dosage forms. 1997, http://www.fda.gov/cder/guidance/1713bp1.pdf (accessed June 2004).

Guinchedi, P.; Maggi, L.; Sangalli, A.; La Manna, A.; Conte U. Hydrophilic matrices for linear (zero-order) extended release of water-insoluble drugs. In: Proceedings of the 11th Pharmaceutical Technology Conference. 1989, 112–121.

Hamdani, J.; Moës, A.J.; Amighi, K. Development and evaluation of prolonged release pellets obtained by the melt pelletization process. International Journal of Pharmaceutics. 2002, 245, 167–177.

Hancock, B.C.; Zografi, G. Characteristics and significance of the amorphous state in pharmaceutical systems. Journal of Pharmaceutical Sciences. 1997, 86, 1–12.

Hemati, M.; Cherif, R.; Saleh, K.; Pont, V. Fluidized bed coating and granulation: influence of process-related variables and physicochemical properties on the growth kinetics. Powder Technology. 2003, 130 (1-3), 18-34.

Heng, P.W.S.; Liew, C.V.; Gu, L. Influence of teardrop studs on rotating frictional base plate on spheroid quality in rotary spheronization. International Journal of Pharmaceutics. 2002, 241, 173–184.

Heng, P.W.S.; Wong, T.W.; Cheong, W.S. Investigation of melt agglomeration process with a hydrophobic binder in combination with sucrose stearate. European Journal of Pharmaceutical Sciences. 2003, 19, 381–393.

Henrist, D.; Remon, J.P. Influence of the formulation composition on the in vitro characteristics of hot stage extrudates. International Journal of Pharmaceutics. 1999a, 188 (1), 111-119.

Henrist, D.; Remon, J.P. Influence of the process parameters on the characteristics of starch based hot stage extrudates. International Journal of Pharmaceutics. 1999b, 189 (1), 7-17.

Higuchi, T. Rate of release of medicaments from ointment bases containing drugs in solution. Journal of Pharmaceutical Sciences. 1961, 50, 874-875.

Higuchi, T. Mechanism of sustained-action medication. Journal of Pharmaceutical Sciences. 1963, 52, 1145-1149.

Hincal, Al; Kas, H.S. Preparation of micropellets by spray congealing. In *Multiparticulate Oral Delivery*, 1st Ed.; Ghebre-Sellassie, I., Ed.; Marcel Dekker: New York, 1994; Vol. 65, 11-34.

Holm, P. High shear mixer granulators. In *Handbook of Pharmaceutical Granulation Technology, Drugs and Pharmaceutical Science*, 1st Ed.; Parikh, D.M., Ed.; Marcel Dekker; New York, 1997; 151–204.

Hülsmann, S.; Backensfeld, T.; Keitel, S.; Bodmeier, R. Melt extrusion—an alternative method for enhancing the dissolution rate of 17-extradiol hemihydrate. European Journal of Pharmaceutics and Biopharmaceutics. 2000, 49, 237-242.

Johansen, A.; Schæfer, T. Effects of interactions between powder particle size and binder viscosity on agglomerate growth mechanisms in a high shear mixer. European Journal of Pharmaceutical Science. 2001, 12, 297–309.

Johansson, B.; Wikberg, M.; Ek, R.; Alderborn, G. Compression behaviour and cmpactability of microcrystalline cellulose pellets in relationship to their pore structure and mechanical properties. International Journal of Pharmaceutics. 1995, 117 (1) 57-73.

Katzhendler, I.; Hoffman, A.; Goldberger, A.; Friedman, M. Modeling of drug release from erodible tablets. Journal of Pharmaceutical Sciences. 1997, 86 (1), 110-115.

Khare, A.R.; Peppas, N.A. Swelling/deswelling of anionic copolymer gels. Biomaterials. 1995, 16, 559–567.

Kidokoro, M.; McGinity, J.W. Properties of tablets containing granulations of ibuprofen and acrylic copolymer prepared by thermal processes. Pharmaceutical Development and Technology. 2001, 6, 263-275.

Korsmeyer, R.W.; Gurny, R.; Doelker, E.M.; Buri, P.; Peppas, N.A. Mechanism of solute release from porous hydrophilic polymers. International Journal of Pharmaceutics. 1983, 15 (1), 25–35.

Kühl, P.; Mielck, J. Tabletting of pellet–matrix systems: ability of parameters from dynamic and kinetic models to elucidate the densification of matrix formers and of pellets. International Journal of Pharmaceutics. 2002, 248 (1-2), 101-114.

Lee, P.I. Diffusion-controlled matrix systems. In *Treatise on Controlled Drug Delivery*, Kydonieus, A., Ed.; Marcel Dekker: New York, 1992; 155-195.

Levis, S.R.; Deasy, P.B. Pharmaceutical applications of size reduced grades of surfactant co-processed microcrystalline cellulose. International Journal of Pharmaceutics. 230, 25-33.

Lippold, B.C.; Pagés, R.M. Film formation, reproducibility of production and curing with respect to release stability of functional coatings from aqueous polymer dispersions. Die Pharmazie. 2001, 49, 243-252.

Liu, J.; Zhang, F.; McGinity, J.W. Properties of lipophilic matrix tablets containing phenylpropanolamine hydrochloride prepared by hot-melt extrusion. European Journal of Pharmaceutics and Biopharmaceutics. 2001, 52, 181-190.

Lundqvist, Å.E.K.; Podczeck, F.; Newton, J.M. Compaction of, and drug release from, coated drug pellets mixed with other pellets. European Journal of Pharmaceutics and Biopharmaceutics. 1998, 46, 369-379.

Maggi, L.; Evelyn, O.M.; Torre, M.L.; Conte, U. Formulation of biphasic release tablets containing slightly soluble drugs. European Journal of Pharmaceutics and Biopharmaceutics. 1999, 48 (1), 37-42.

Mahaguna, V.; Talbert, R.L.; Peters, J.I.; Adams, S.; Reynolds, T.D.; Lam, F.Y.W.; Williams, R.O., III. Influence of hydroxypropyl methylcellulose polymer on in vitro and in vivo performance of controlled release tablets containing alprazolam. European Journal of Pharmaceutics and Biopharmaceutics. 2003, 56 (3), 101-108.

Mehta, K.A.; Kislalioglu, M.S.; Phuapradit, W.; Malick, A.W.; Shah, N.H. Release performance of a poorly soluble drug from a novel, Eudragit-based multi-unit erosion matrix. International Journal of Pharmaceutics. 2001, 213, 7-12.

McGinity, J.W., Koleng, J.J., Repka, M.A. and Zhang, F., 2000, Hot-melt extrusion technology. In *Encyclopedia Pharmaceutical Technology,* 2nd Ed.; Swarbrick, J.; Boilan, J.C., Eds.; Marcel Dekker: New York, 2000, Vol. 19, 203-226.

McGinity, J.W.; Zhang, F. Melt-extruded controlled-release dosage forms. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 183-208.

Nakahara. U.S. Patent 3,277,520, October 1966.

Nellore, R.V.; Gurvinder, S.R.; Hussain, A.S.; Tillman, L.G.; Augsburger, L.L., Development of metoprolol tartrate extended-release matrix tablet

formulations for regulatory policy consideration. Journal of Controlled Release. 1998, 50 (1-3), 247-256.

Nicklasson, F.; Alderborn, G. Modulation of the tabletting behaviour of microcrystalline cellulose pellets by the incorporation of polyethylene glycol. European Journal of Pharmaceutical Sciences. 1999, 9 (1), 57-65.

Omelczuk, M.O.; McGinity, J.W. The influence of thermal treatment on the physical-mechanical and dissolution properties of tablets containing poly(dl-lactic acid). Pharmaceutical Research. 1993, 10, 542-548.

Onay-Basaran, S.; Olsen, J. Formulation of long acting quinacrine hydrochloride pellets in different matrices. Part 1. Drug Development and Industrial Pharmacy. 1985, 11, 2143-2154.

Peppas, N.A. Analysis of Fickian and non-Fickian drug release from polymers. Pharmceutica Acta Helvetiae. 1985, 60 (4), 110–111.

Perdikoulias, J.; Dobbie, T. Die design. In *Pharmaceutical Extrusion Technology*, 1st Ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker: New York, 2003; Vol. 133, 99-110.

Perez-Marcos, B.; Gutierrez, C.; Gomez-Amoza, J.L.; Rartinez-Pacheco, R.; Souto, C.; Concherio, A. Usefulness of certain varieties of Carbomer in the formulation of hydrophilic furosemide matrices. International Journal of Pharmaceutics. 1991, 67 (2), 113–121.

Perez-Marcos, B.; Ford, J.L.; Armstrong, D.J.; Elliott, P.N.C.; Rostron, C.; Hogan, J.E. Release of propranolol hydrochloride from matrix tablets containing hydroxypropylmethylcellulose K4M and carbopol 974. International Journal of Pharmaceutics. 1994, 111 (3), 251-259.

Picker, K.M.; Bikane, F. Tablet formation and release from matrix tablets manufactured with cellulose acetate. International Journal of Pharmaceutics. 1998, 175 (2), 147-164.

Porter, S. Coating of pharmaceutical dosage forms. In *Remington: the Science and Practice of Pharmacy,* Limmer, D., Ed.; Lippincott: Baltimore, 2000, 894-902.

Pose-Vilarnovo, B.; Rodríguez-Tenreiro, C.; Santos, J.F.; Vázquez-Doval, J.; Concheiro, A.; Alvarez-Lorenzo, C.; Torres-Labandeira, J.L. Modulating drug release with cyclodextrins in hydroxypropyl methylcellulose gels and tablets. Journal of Controlled Release. 2004, 94 (2-3), 351-363.

Rauwendaal, C. *Polymer Extrusion*, 3rd Ed.; Hanser: New York, 1994; 15-48.

Repka, M.A.; Gerding, T.G.; Repka, S.L.; McGinity, J.W. Influence of plasticizers and drugs on the physical-mechanical properties of hydroxypropylcellulose films prepared by hot-melt extrusion. Drug Development and Industrial Pharmacy.1999, 25, 625–633.

Repka, M.A.; McGinity, J.W. Influence of Vitamin E TPGS on the properties of hydrophilic films produced by hot-melt extrusion. International Journal of Pharmaceutics. 2000, 202, 63-70.

Repka, M.A.; McGinity, J.W. Physical-mechanical, moisture absorption and bioadhesive properties of hydroxypropylcellulose hot-melt extruded films. Biomaterials. 2000, 21, 1509-1517.

Repka, M.A.; Repka, S.L.; McGinity, J.W. Bioadhesive hot-melt extruded film for topical and mucosal adhesion applications and drug delivery and process for preparation thereof.. US Patent 6,375,963, 2002.

Reynolds, A.D. A new technique for the production of spherical particles. Manufacturing Chemist and Aerosol News. 1970, 41, 40-43.

Ritger, P.L.; Peppas, N.A. A simple equation for description of solute release II. Fickian and anomalous release from swellable devices. Journal of Controlled Release. 1987, 5 (1), 37–42.

Ritschel, W.A. Pharmacokinetic and biopharmaceutical aspects in drug delivery. In: Tyle, P. (Ed.), Drug Delivery Devices: Fundamentals and Applications. Marcel Dekker, New York, 1988, 19–79.

Ritschel, W.A., Biopharmaceutic and pharmacokinetic aspects in the design of controlled release peroral drug delivery systems. Drug Development and Industrial Pharmacy. 1989, 15, 1073–1103.

Rubio, M.; Ghaly, E. In vitro release of acetaminophen from sodium alginate controlled release pellets. Drug Development and Industrial Pharmacy. 1994, 20, 1239-1251.

Sandberg, A.; Blomqvist, I.; Jonsson, U.; Lundborg, P. Pharmacokinetic and pharmacodynamic properties of a new controlled-release formulation of metoprolol: a comparison with conventional tablets. European Journal of Clinical Pharmacology. 1988, 33 (Suppl.), S9–S14.

Sarisuta, N.; Punpreuk, K. In vitro properties of film-coated diltiazem hydrochloride pellets compressed into tablets. Journal of Controlled Release. 1994, 31 (3), 215-222.

Shah, N.; Zhang, G.; Apelian, V.; Zheng, F.; Infield, M.H.; Mallick, A.W. Prediction of drug release from hydroxypropyl methylcellulose (HPMC) matrices: effect of polymer concentration. Pharmaceutical Research. 1993, 10 (11), 1693–1695.

Sinha, V.; Trehan, A., 2003, Biodegradable microspheres Sato, H.; Miyagawa, Y.; Okabe, T.; Miyajima, M.; Sunada, H., Dissolution mechanism of diclofenac sodium from wax matrix granules. Journal of Pharmaceutical Sciences. 1997, 86(8), 929-934.

Schæfer, T.; Mathiesen, C. Melt pelletization in a high shear mixer. IX. Effects of binder particle size. International Journal of Pharmaceutics. 1996, 139, 139–148.

Sears, J.K.; Darby, J.R. *The Technology of Plasticizer*. John Wiley & Sons: New York, 1982.

Seo, A.; Schæfer, T. Melt agglomeration with polyethylene glycol beads at a low impeller speed in a high shear mixer. European Journal of Biopharmaceutics. 2001, 52, 315–325.

Siepmann, J.; Podual, K.; Sriwongjanya, M.; Peppas, N.A.; Bodmeier, R. A new model describing the swelling and drug release kinetics from hydroxypropyl methylcellulose tablets. Journal of Pharmaceutical Sciences. 1999, 88 (1), 65-72.

Siepmann, J.; Kranz, H.; Peppas, N.A.; Bodmeier, R. Calculation of the required size and shape of hydroxypropyl methylcellulose matrices to achieve desired drug release profiles. International Journal of Pharmaceutics. 2000, 201 (2), 151-164.

Siepmann, J.; Peppas, N.A. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Advanced Drug Delivery Reviews. 2001, 48 (2-3), 139-157.

Sinha, V.; Trehan, A., 2003, Biodegradable microspheres for protein delivery. Journal of Controlled Release. 2002, 90 (3), 261-280.

Sood, A.; Panchagnula, R. Design of controlled release delivery systems using a modified pharmacokinetic approach: a case study for drugs having a short elimination half-life and a narrow therapeutic index. International Journal of Pharmaceutics. 2003, 261 (1-2), 27-41.

Sprockel, O.L.; Sen, M.; Shivanand, P.; Prapaitrakul, W. A melt-extrusion process for manufacturing matrix drug delivery systems. International Journal of Pharmaceutics. 1997, 155, 191-199.

Struik, L.E. *Physical aging of amorphous polymers and other materials*. Elsiver: New York, 1978.

Sung, K.C.; Nixon, P.R.; Skoug, J.W.; Ju, T.R.; Gau, P.; Topp, E.M.; Patel, M.V. Effect of formulation variables on drug and polymer release form HPMC-based matrix tablets. International Journal of Pharmaceutics. 1996, 142 (1), 53–60.

Suzuki, H.; Sunada, H. Influence of water-soluble polymers on the dissolution of nifedipine solid dispersions with combined carriers. Chemical and Pharmaceutical Bulletin. 1997, 45, 1688–1693.

Tongwen, X.; Binglin, H. Mechanism of sustained drug release in diffusion-controlled polymer matrix-application of percolation theory. International Journal of Pharmaceutics. 1998, 170, 139-149.

Torrado, J.; Augsburger, L. Effect of different excipients on the tableting of coated particles. International Journal of Pharmaceutics. 1994, 106 (2), 149-155.

Tunón, Å; Alderborn, G. Granule deformation and densification during compression of binary mixtures of granules. International Journal of Pharmaceutics. 2001, 222 (1), 65-76.

Tunón, Å.; Gråsjö, J.; Alderborn, G. Effect of intragranular porosity on compression behaviour of and drug release from reservoir pellets. European Journal of Pharmaceutical Sciences. 2003, 19 (5), 333-344.

Van Krevelen, D.W.; Hoftyzer, P.J. *Properties of Polymers*, 3rd Ed.; Elsevier: Amsterdam, 1990.

Varner, J. Descriptive fractography, ceramics and glasses. Engineered Materials Handbook. 1991, 4, 634-644.

Vazquez, M.J.; Casalderrey, M.; Duro, R.; Gomez-Amoza, J.L.; Martinez-Pacheco, R., Souto, C.; Concheiro, A., Atenolol release from hydrophylic matrix tablets with hydroxypropylmethyl cellulose (HPMC) mixtures as gelling agent: effects of the viscosity of the HPMC mixture. European Journal of Pharmaceutical Sciences. 1996, 4 (1), 39–48.

Vergote, G.J.; Vervaet, C.; Van Driessche, I.; Hoste, S.; De Smedt, S.; Demeester, J.; Jain, R.A.; Ruddy, S.; Remon, J.P. An oral controlled release matrix pellet formulation containing nanocrystalline ketoprofen, International Journal of Pharmaceutics. 2001, 219, 81-87.

Vogel, A.I.; Furniss, B.S.; Hannaford, A.J.; Smith, P.W.G.; Tatchell, A.R. *Textbook of Practical Organic Chemistry*, 5th Ed.; Addison-Wesley: London, 1996.

Wagner, K.; Krumme; M., Beckert, T.; Schmidt, P. Development of disintegrating multiple-unit tablets on a high-speed rotary tablet press. European Journal of Pharmaceutics and Biopharmaceutics. 2000, 50, 285-292.

Wan, L.; Heng, P.; Ling, B.L.; Effect of polyvinylpyrrolidone solutions containing dissolved drug on characteristics of lactose fluidized bed granules. International Journal of Pharmaceutics. 141 (1-2), 1996, 161-170.

Wheatley, T.A.; Steuernagel, C.R. Latex emulsions for controlled drug delivery. In *Aqueous Polymeric Coating for Pharmaceutical Dosage Forms*, McGinity, J.W., Ed.; Marcel Dekker: New York, 1997; Vol. 79, 19-41.

Wicks, Z.W. Free volume and coatings formulator. Journal of Coatings Technology, 1986, 58, 23-32.

Wu, C.; McGinity, J.W. Non-traditional plasticization of polymeric films. International Journal of Pharmaceutics. 1999, 177, 15–27.

Young, C.R.; Koleng, J.J.; McGinity, J.W. Properties of drug-containing spherical pellets produced by a hot-melt extrusion and spheronization process. Journal of Microencapsulation. 2003, 20 (5), 613-625.

Young, C.R.; Koleng, J.J.; McGinity, J.W. Production of spherical pellets by a hot-melt extrusion and spheronization process. International Journal of Pharmaceutics. 2002, 242 (1-2), 87-92.

Zhang, F.; McGinity, J.W. Properties of sustained release tablets prepared by hot-melt extrusion. Pharmaceutical Development and Technology. 1999, 4, 241–250.

Zhang, F.; McGinity, J.W. Properties of hot-melt-extruded theophylline tablets containing poly(vinyl acetate). Drug Development and Industrial Pharmacy. 2000, 26, 931-942.

Zhang, Y.E.; Tchao, R.; Schwartz, J.B. Effect of processing methods and heat treatment on the formation of wax matrix tablets for sustained drug release. Pharmaceutical Development and Technology. 2001, 6, 131-144.

Zhang, Y.; Zhang, Z.; Wu, F. A novel pulsed-release system based on swelling and osmotic pumping mechanism. Journal of Controlled Release. 2003, 89 (1), 47-55.

Zhu, Y.; Shah, N.H.; Malick, A.W.; Infeld, M.H.; McGinity, J.W. Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. International Journal of Pharmaceutics, 2002, 241(2), 301-310.

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